World Premier International Research Center Initiative (WPI)
FY 2019 WPI Project Progress Report

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Research Center	International Institute for Integrative Sleep Medicine (IIIS)		
Center Director	Masashi Yanagisawa	Administrative Director	Toshio Kokubo

Common instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2020) situation of your WPI center.
* So as to execute this fiscal year's follow-up review on the "last" center project plan, prepare this report based on it.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

- 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. Advancing Research of the Highest Global Level

Lack of sound sleep causes not only a reduction in higher-order brain functions including memory and decision making, but also increases risks of a number of diseases such as depression and metabolic syndrome. Further, in developed countries, the prevalence rate of sleep disorders is around 15%, with the lifetime prevalence more than 30%. The deficiencies in healthy sleep cause significant social losses as well. According to RAND Europe, the economic loss due to the sleep deficiencies in Japan corresponds to 2.92% of GDP, the worst in the world. It is indeed the urgent need to solve sleep-related issues. We thus set out our major objectives of our sleep research as follows.

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

To address the first objective, we dissect neuronal and molecular mechanisms of sleep regulation to elucidate operating principles of neural networks regulating sleep, wake and their transitions. We also use an unbiased genetic approach to identify novel genes involved in the sleep/wake regulation.

As for the second objective, we study pathogenesis of sleep disorders and related mental diseases including phobia and anxiety, using genetically engineered mouse models. We have also expanded our human physiological studies of sleep by the establishment of Human Sleep Lab.

To achieve the third objective, we have been developing lead compounds of novel drugs modulating sleep and wake. We are also developing an EEG-measuring-wearable device and sleep staging algorithms based on the artificial intelligence for the sleep measurement at home.

This fiscal year, the Vice Center Director found a group of neurons in hypothalamus whose forced-activation induces hibernation in mice. Besides sleep, hibernation is another behavior that is characterized by regulated hypomobility. Revealing similarities and differences between sleep and hibernation would lead us to better understanding of both hypomobile behaviors. We have thus added the following goal as the fourth objective of our research in IIIS.

4. To elucidate the fundamental mechanisms of hibernation regulation

To achieve these objectives, we continue the efforts to secure sufficient external research funds and to increase and expand collaboration/research alliances especially in the field of translational research with outside groups including the collaboration groups in University of Tsukuba, the Satellites, external research institutions, and many companies.

2. Generating Fused Disciplines

To achieve 4 objectives shown above, we have to conduct wide-ranging sleep research, covering a scope from basic biology to pharmaceutical science and further to experimental medicine. It is the new fused discipline, "sleep science," we aim to generate by merging 3 research fields.

Collaborative research among labs in IIIS is crucial to realize "sleep science," and the internal collaborations are becoming active owing to physically and psychologically open atmosphere created/enhanced by the open structure of the IIIS Building and the open communication through unique meetings such as the Work in Progress meeting, the Dojo journal club, and Brie & Bordeaux.

In addition to the studies of drug discovery, collaborations between labs in different disciplines have enabled translational studies, *e.g.*, comparing effects of an orexin antagonist and a $GABA_A$ agonist on human physical and cognitive functions, developing a system for the sleep measurement at home, and developing Mobile Sleep Lab by remodeling a fuel cell bus.

3. Realizing an International Research Environment

We continue active collaborations with 3 Satellite PIs in University of Texas Southwestern Medical Center, while a new collaboration agreement was executed with National Institute of Biological Sciences, Beijing for the cross-appointment of Q. Liu, who serves as the 1st overseas Satellite PI of IIIS in Asia. The overseas Satellite PIs visit Tsukuba regularly to actively participate in important events such as the Site Visit and Annual IIIS Symposium.

We hosted 19 WPI-IIIS Seminars in FY 2019, for which 9 speakers were invited from abroad (47%). The 8th IIIS Symposium, jointly hosted by the Ph.D. Program in Humanics, was held in Tokyo in conjunction with the 36th Takamine Conference. Invited speakers included internationally recognized neuroscientists, and over 200 researchers and students participated in the conference.

To further strengthen our international research environment, we continuously seek scientists internationally. In FY 2019 we recruited three researchers from overseas (two from China and one from the USA), while, after the career at IIIS, several young researchers took overseas opportunities, including a senior research fellow (PI) at Harbin Institute of Technology, a researcher at Shenzhen University College of Materials, and a postdoc each in Harvard Medical School and Fred Hutchinson Cancer Research Center. Furthermore, one of our junior PIs was promoted to a full professor at Kyoto University. Research achievements and experiences at IIIS contribute to career development and accelerating the international circulation of talented researchers.

4. Making Organizational Reforms

We have made significant efforts to improve administration systems, rules and bylaws of University of Tsukuba to realize objectives/policies of IIIS and the WPI program. Our recent efforts to make organizational reforms are focused on supporting young researchers and students, *e.g.*, introducing an internal grant system, creating a new RA system, starting a new scholarship, continuing the mental care program for students. Further, we have recently introduced the online residence application procedures for the first time in the university.

As a part of the various supports by the host institution, as of March 26, 2020, the university officially established Organization for Development of Global Research Centers, accommodating IIIS and 2 world-class research centers, CCS and TARA-Center, to expand horizontally among these centers the achievements of organizational reforms thus far headed by IIIS.

5. Efforts to Secure the Center's Future Development over the Mid- to Long-term

The expansion of the research scope from sleep to hypomobile behaviors requires expansion of research organization as well. We shall enlarge the research capacity to spare appropriate research resources for hibernation studies. The research organization for the sleep research shall be also expanded to accommodate studies of system biology and AI. We thus seek alternative financial resources that substitute for the WPI program aggressively, in combination of several funding programs, grants, donations and IP incomes, rather than a single source of financial support.

Since IIIS has been built up as a *de novo* WPI center, most of PIs have been appointed as a contract employee with a limited term. In order to keep qualified PIs and make IIIS sustainable, we have to grant tenure to them before 10 years of the term completes. As the President of University of Tsukuba has repeatedly stated, PIs with a proven track record of achievements shall be nominated by the Center Director and subjected to the tenure review.

6. Others

In order to enhance the visibility of IIIS, we conduct various outreach activities, *e.g.*, opening a booth to promote our research achievements in several science events for general public, joining an on-site event of the internet broadcasting, Nico Nico Cho-Kaigi, accepting visitors from junior/senior high schools, and holding IIIS Open House for administrative staffs in the headquarters of University of Tsukuba to promote better internal understanding of IIIS.

A new Ph.D. program in Humanics, which is led by the Center Director as the Principal Coordinator, was adopted in October 2018 for WISE Program of MEXT. It aims to create a new academic discipline to merge high levels of expertise in biomedical sciences and physical sciences/engineering/informatics. Seven out of 24 students enrolled in FY 2019-2020 have selected PIs in IIIS as one of their dual-mentors for dissertation studies, showing great appeal of the sleep research to students.

* Describe clearly and concisely the progress being made by the WPI center project from the viewpoints below.
- In addressing the below-listed 1-6 viewpoints, 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 disciplines).
  (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. Advancing Research of the Highest Global Level

* Among the research results achieved by the center, concretely describe those that are at the world's highest level. In Appendix 1, list the center's research papers published in 2019.
* Regarding the criteria used when evaluating the world level of center, 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*

This fiscal year, Vice Center Director of IIIS, T. Sakurai and his colleague found a group of neurons in hypothalamus that induce hibernation in mice by chance. Besides sleep, hibernation is another behavior that is characterized by regulated hypomobility. The fundamental mechanisms of hibernation are also unknown, although it is known that 183 species, e.g., bears, chipmunks, lemurs (a primate) and bats, among about 4,100 species of mammals hibernate. Similarities and differences between sleep and hibernation would help our understanding of both hypomobile behaviors. We thus decided to add the fourth major objective of sleep research in IIIS.

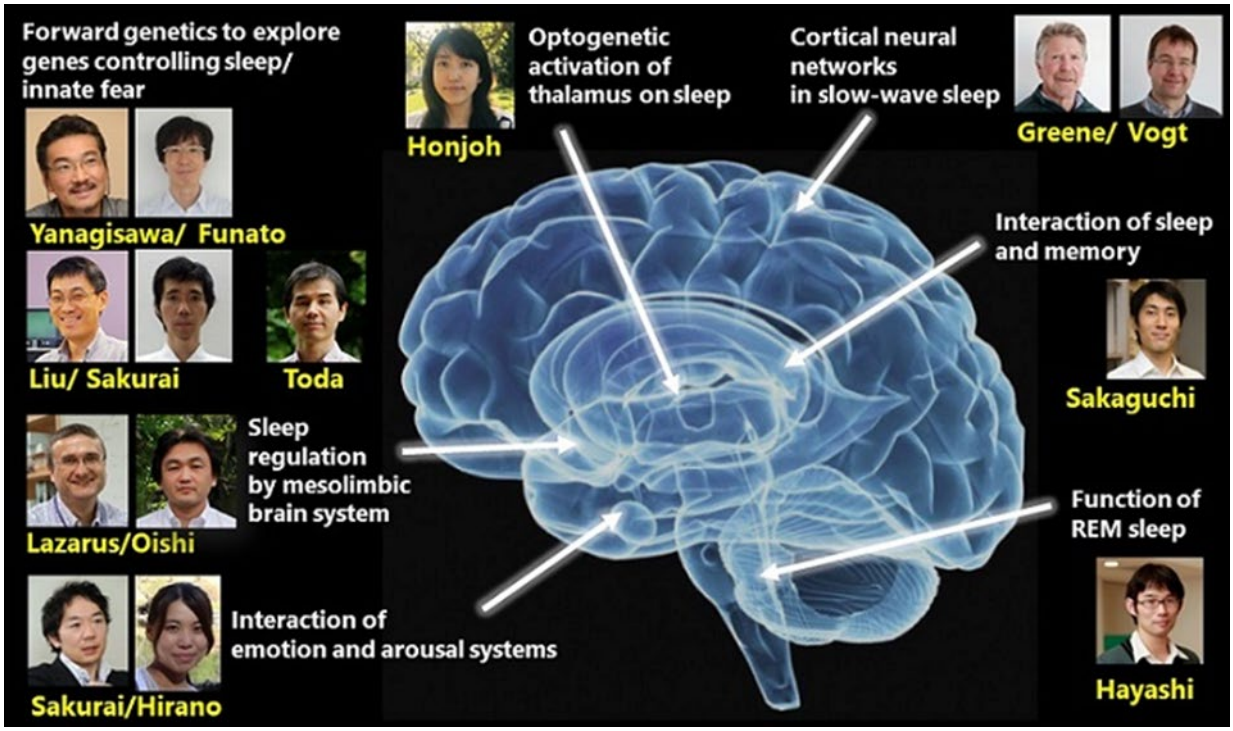
4. *To elucidate the fundamental mechanisms of hibernation regulation*

It would be an interesting question whether we need sleep during the period of hibernation. We will also study the interaction between sleep and hibernation.

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

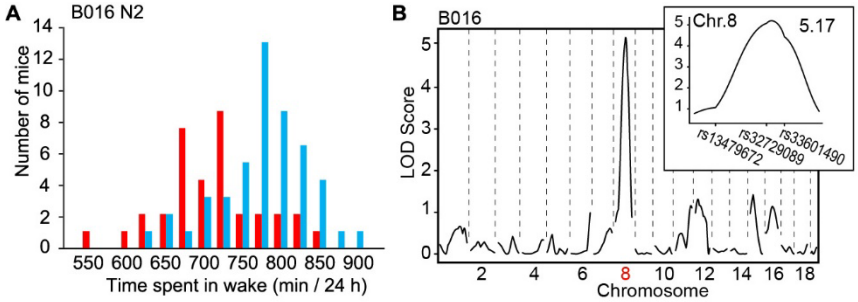
We dissect neuronal and molecular mechanisms of sleep regulation to elucidate operating principles of neural networks regulating sleep/wakefulness as well as sleep-related mental activities such as emotion and memory. There are multiple brain regions and nuclei responsible for sleep/wake regulation such as hypothalamus, amygdala, the nucleus accumbens, cortical neural networks, the brainstem pons, hippocampus, thalamus, etc. PIs studying neuroscience share target regions and nuclei to avoid overlapping.

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/wakefulness.



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

We have been conducting forward genetic research which led to the identification of a protein kinase SIK3 and leak cation channel NALCN as novel regulators of NREM sleep and REM sleep, respectively (Funato *et al.*, Nature, 2016). *Sleepy* mutant pedigree that have a splice mutation in *Sik3* gene causing the skipping of exon13 is characterize by increased NREM sleep amount and increased sleep need. The exon 13-encoded region contains a phylogenetically conserved PKA phosphorylation site (Ser551). As published in the previous fiscal year, $Sik3^{S551A/+}$ and $Sik3^{S551D/+}$ mice showed an increased total NREM sleep time, a decreased total wake time and unaltered REM sleep time compared with wild-type littermates (Honda *et al.*, Proc Natl Acad Sci USA, 2018). Neuron-specific *Sik3* deficiency may decrease sleep need (Asano *et al.* in preparation). This result strongly suggests that the PKA-SIK3 pathway constitute an enigmatic intracellular signaling regulating sleep. Further studies on other SIK family members, SIK1 and SIK2 broaden and confirm the



Gene	*Tex15*	*Pik3r2*	*Cacna1a*	*Zfp423*
GRCm38	33581475	70772570	84461494	87904442
Base change	T to C	G to C	T to C	C to T
Function	Intron	Intron	Exon	Intron
Wake time				
B016ABF10104 516	○	×	○	○
B016ABF10501 526	○	×	○	×
B016ABF10206 530	×	○	○	○
B016ABF10702 534	○	○	○	×
B016ABF10401 542	○	×	○	×
B016ABF10601 546	×	×	○	×
B016ABF10302 547	○	×	○	○
B016ABF10301 568	×	×	×	×
N2 control	×	×	×	×

Fig. 1. Identification of the *Cacna1a* gene mutation in the *Drowsy* pedigree showing a heritable but weak sleep phenotype. (A) Wake time distribution of retrospectively genotyped *Drowsy* N2 littermates. $Cacna1a^{+/+}$ (blue) and $Cacna1a^{m/+}$ (red) mice. (B) QTL analysis of the *Drowsy* pedigree for total wake time (n = 81). (Inset) LOD score peak between rs13479672 and rs33601490 on chromosome 8. (C) Mutational analysis of affected mice (bottom 20% in total wake time) and unaffected mice (top 20% in total wake time) within the *Drowsy* pedigree. (D) Structure of the CACNA1A protein indicating the F102L mutation (this study; pink), together with examples of human missense mutations reported in familial hemiplegic migraine (yellow) and episodic ataxia type2 (green), as well as the polyglutamine repeat found in spinocerebellar ataxia type 6 (Gln).

PKA-SIK pathway as a crucial signaling for sleep need encoding (Park *et al.*, in submission). Induction of *Sik3*^{Sleepy} allele in neurons in late infancy increases sleep need (Iwasaki *et al.*, in submission). 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). In addition to *Sleepy* pedigree, we are working on characterizing *Sleepy2* pedigree (Kim *et al.,* in preparation).

These discoveries proved that we can identify physiologically relevant findings through the dominant screening of randomly mutagenized mice for sleep. We have developed and improved our in-house dominant screening workflow that can be applied for a variety of phenotypes including behavior, metabolism and immunology (Miyoshi *et al.*, Proc Natl Acad Sci USA, 2019). In our screening, C57BL/ 6J (B6J) and C57BL/6N (B6N) are chosen as mutagenized and counter strains, respectively. As for the reproducibility of sleep parameters, the total time spent in the wake and NREMS, as well as the REMS episode duration, shows sufficient reproducibility with small coefficients of variance, indicating that these parameters are most suitable for quantitative phenotype-driven screening.

In addition to *Sleepy* and *Sleepy2*, we established *Drowsy* pedigree that showed moderate hypersomnolence (Fig. 1) (Miyoshi *et al.*, Proc Natl Acad Sci USA, 2019). Linkage analysis and whole exome sequencing identified a missense mutation in the *Cacna1a* gene in almost all long sleep individuals. Homozygous mutant mice exhibited severe motor abnormality with abnormal posture and loss of motor coordinate. CACNA1A is a voltage-dependent calcium channel that is abundantly expressed in the cerebellum and spinal cord. *Drowsy* mutant mice have a heterozygous mutation for *Cacna1a* gene. Thus, haploinsufficiency of *Cacna1a* gene changes sleep amount, which suggests the role of calcium signaling in sleep/wakefulness regulation.

(2) Understanding the biological clock regulating sleep/wake rhythms at cellular and molecular levels (Sakurai/Hirano Lab)

The circadian clock is one of major biological systems controlling sleep/wake behavior, thus the circadian rhythms disorder is highly associated with sleep disorder. The master clock coordinating biological rhythms is located in suprachiasmatic nucleus (SCN) in the hypothalamus. Although molecular mechanism of the clock oscillation in each SCN neuron has been well studied, heterogeneity of SCN-composing neurons and its biological function have been largely unknown. We have performed anatomical analysis of the SCN by using several Cre driver mouse lines and investigated functions of specific neurons characterized by neuropeptides in regulation of the sleep rhythms. We demonstrated that AVP neurons has a significant role in neuronal coupling within the SCN (Mieda *et al.*, Neuron, 2015) and that Neuromedin S neurons are essential to generate sleep rhythms (Lee *et al.*, Neuron, 2015). We also demonstrated that GRP neurons in the SCN has essential role in rhythmic behavioral output, while they compose of relatively small population in the SCN (unpublished). By using retrograde tracing method, we succeeded to label SCN neurons projecting to a specific region and evaluated the physiological function of these neurons. We figured out the neural pathway from SCN neurons important for sleep/wake regulation (unpublished).

Furthermore, by using forward genetics in humans showing familial sleep disorder, we have identified novel molecular mechanisms of the circadian sleep regulation, which is well conserved in mice and humans (Hirano *et al.*, Proc Natl Acad Sci USA, 2018). We demonstrated that dysfunction of the clock regulatory system found in human sleep disorder also disrupts circadian glucose metabolism in mice (Hirano *et al.*, Cell Reports, 2017). Our studies focusing on the circadian clock have advanced the understanding how the biological clock regulates sleep and metabolism, potentially leading to clinical applications.

(3) The gating of sleep by motivation (Lazarus/Oishi Lab)

The brain mechanisms governing the regulation of sleep by cognitive and emotional factors are not well understood. The Lazarus/Oishi laboratory recently revealed a prominent role of adenosine A_{2A} receptor ($A_{2A}R$)-expressing indirect pathway neurons in the nucleus accumbens (NAc) in sleep/wake regulation and proposed a

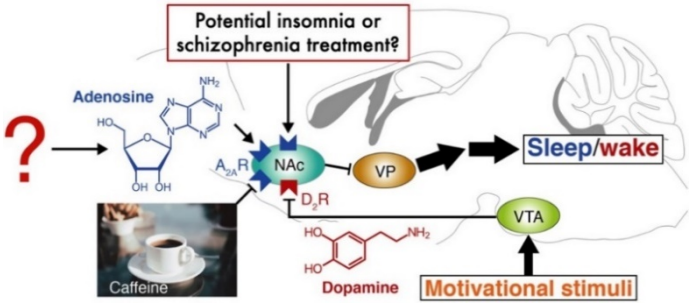


Fig. 2. Sleep control by motivation.

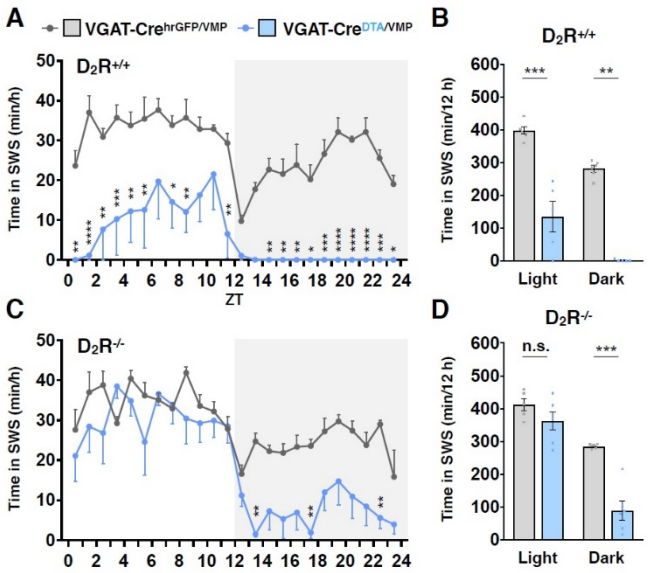


Fig. 3. Dopamine D_2R mediate sleep reduction induced by GABAergic VMP ablation. Hourly (A,C) or total (B,D) SWS amounts in $D_2R^{+/+}$ (A,B) or $D_2R^{-/-}$ (C,D) mice demonstrating that D_2R mediate the ablation-induced SWS reduction in the light period.

novel brain circuit for sleep control by motivation (Fig. 2; Oishi *et al.*, Nature Commun, 2017; Altmetric score: 355). This brain circuit may explain the tendency to fall asleep in the absence of motivating stimuli, i.e., when bored. The classic somnogen adenosine is a plausible 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. Moreover, 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). In addition, the Lazarus/Oishi lab revealed that elevated adenosine levels in the NAc promote slow-wave sleep (SWS) via $A_{2A}R$ (Zhou *et al.*, Neurochem Int, 2019). The source of the released adenosine, however, remains controversial. Some of the adenosine may originate from astrocytes and some may originate from neurons or even microglia, but direct proof is lacking and thus the exact source of adenosine remains unknown.

Adenosine acting on NAc $A_{2A}R$ stimulates original thinking of new opportunities for insomnia and schizophrenia pharmacotherapy. However, due to the lack of brain permeability, all currently existing $A_{2A}R$ agonists are not suitable for treating the central nervous system. The possibility that $A_{2A}R$ responses in the brain can be achieved by using allosteric modulators has been largely ignored. A positive allosteric modulator may evoke selective physiologic $A_{2A}R$ responses because, in contrast to an $A_{2A}R$ agonist, its actions are limited to when and where adenosine is released at physiologically relevant concentrations. The Lazarus/Oishi lab developed the first positive $A_{2A}R$ allosteric modulator that evokes $A_{2A}R$ responses in the brain, including sleep induction, without affecting cardiovascular function, unlike classic $A_{2A}R$ agonists (Patent applications 2017-202225 and 2019-076477, and Korkutata *et al.*, Neuropharmacology, 2019).

The Lazarus/Oishi lab also discovered a neural circuit in the ventral medial midbrain/pons area (VMP) at the junction of the ventral medial midbrain and pons that controls SWS and wakefulness (Takata *et al.*, J Neurosci, 2018). They used an ablation technique based on the viral expression of diphtheria toxin fragment A (DTA) and found that GABAergic neuron-specific ablations in the VMP largely reduced SWS (Fig. 3A, B). They found that the reduction of SWS was largely diminished in mice lacking dopamine D_2 receptors ($D_2R^{-/-}$), especially during the light period (Fig. 3C,D; unpublished data). These findings indicate that the sleep reduction induced by ablating VMP GABAergic neurons is mainly mediated by D_2R.

(4) Circuit of REM-atonia and cataplexy (Sakurai/Hirano Lab)

During rapid eye movement (REM) sleep, anti-gravity muscle tone and bodily movements are mostly absent, because somatic motoneurons are inhibited by descending inhibitory pathways. Recent studies showed that glycine/GABA neurons in the ventromedial medulla (VMM) (GlyVMM neurons) play an important role in generating the muscle atonia during REM sleep (REM-atonia). However, how these REM-atonia inducing neurons interconnect with other neuronal populations has been unknown. We identified a specific subpopulation of GlyVMM neurons that play an important role in induction of REM-atonia by virus vector-mediated tracing. We found these neurons receive direct synaptic input by neurons in several brain stem regions, including glutamatergic neurons in the sublaterodorsal tegmental nucleus (SLD)(GluSLD neurons). Silencing this circuit by specifically expressing tetanus toxin light chain (TeTNLC) resulted in REM sleep without atonia. This manipulation also caused a drastic decrease in time spent in cataplexy-like episodes when applied to narcoleptic orexin-ataxin-3 mice. We also showed a population of GlyVMM neurons, which is different from REM-atonia-inducing neurons, plays an important role in maintenance of sleep. This present study identified subpopulation of glycinergic neurons in the VMM that are commonly involved

in REM-atonia and cataplexy (Uchida *et al.*, submitted).

Cataplexy is a symptom of narcolepsy type 1, which is caused by degenerative loss of hypothalamic orexin neurons. This is a sudden weakening of postural muscle tone triggered by strong positive emotions such as laughter, joking, and delight. We postulated dopaminergic signaling is involved in cataplexy. We found that dopamine (DA) levels is transiently increased in the amygdala in advance of emergence of cataplexy. Optogenetic manipulation to increase in DA levels in the amygdala mimicking the pattern observed during cataplexy was found to induce cataplexy-like attack even in wild type mice. These observations suggest that transient increase in DA levels in the amygdala triggers cataplexy (Hasegawa *et al.*, manuscript in preparation.)

(5) The functions of REM sleep revealed by its manipulation (Hayashi Lab)

Our sleep is composed of two stages, rapid eye movement (REM) sleep and non-REM sleep. The function of REM sleep, which is the major source of vivid dreams, was one of the largest mysteries in neuroscience. Researchers in IIIS led by Yu Hayashi established transgenic mice in which REM sleep can be shut down at a desired timing without any mechanical stimulus using chemogenetics. Through analyses of this transgenic mouse, it was revealed that REM sleep contributes to generation of slow waves, a brain activity important for learning and memory (Hayashi *et al.*, Science, 2015). Another group of researchers in IIIS led by Michael Lazarus revealed that REM sleep might be important to suppress excess consumption of highly palatable food and that a brain area termed the medial prefrontal cortex is involved (McEown *et al.*, eLife, 2016). These studies reveal novel functions of REM sleep and the underlying mechanisms. Thus, as next steps, it was important to manipulate REM sleep for longer periods to see how it affects our brain maintenance and metabolism. This year, researchers led by Yu Hayashi identified multiple groups of neurons in the brainstem that regulate switching between REM sleep and NREM sleep (Kashiwagi *et al.*, Curr Biol, 2020). By genetic manipulation of these neurons, it was possible to increase REM sleep for lifetime. Moreover, the group discovered that all these neurons produce the neuropeptide neurotensin, and that neurotensin itself is involved in regulating REM and NREM sleep. Thus, future approaches that target the neurotensin receptors may allow non-genetic manipulation of REM and NREM sleep. The group also found that chronic stress strongly affects both the quality and the quantity of REM sleep (Yasugaki *et al.*, Front Neurosci, 2019). Thus, the outcome of manipulating REM sleep under stressed conditions on mental health is another important question to be answered in the future.

(6) Elucidation of the functions of thalamic matrix cells in regulation of cortical activityand arousal (Honjoh Lab)

The neocortex and the thalamus are reciprocally connected and are believed to be critical for arousal and cognitive function. However, the role of thalamus in vigilance state regulation remained elusive, mostly due to technical difficulties. We employed recent techniques, such as optogenetics and chemogenetics, and demonstrated that a thalamic neural subpopulation, matrix cells, promotes behavioral arousal through global cortical activation (Honjoh *et al.*, Nat Commun, 2018). To elucidate how matrix cells promote arousal through cortical activation, we recorded neural activities across sleep/wake cycles in free-behaving mice. To delineate how sleep impacts functional organization of the hierarchical brain system, we decided to perform chronic extracellular recording across the thalamocortical hierarchy, including motor and sensory thalamic nuclei, motor and sensory cortices and higher cortical area. We performed spike sorting and obtained 917 neurons from 21

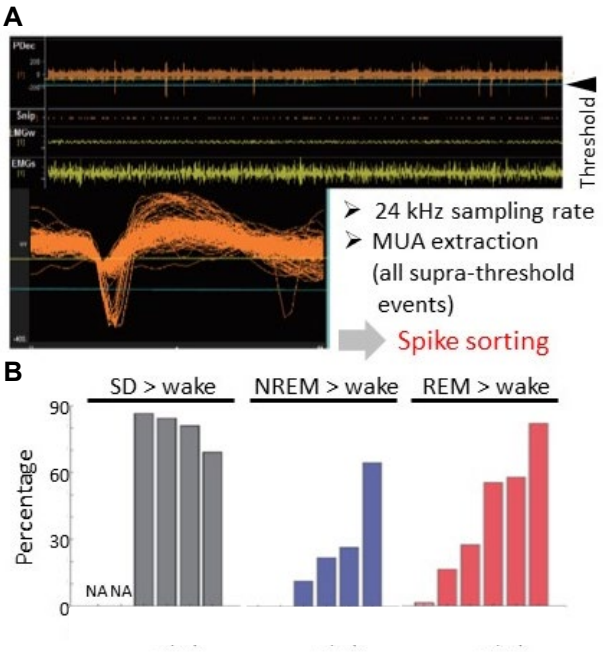


Fig. 4. Thalamocortical neural activity dynamics across sleep/wake cycle. A. An example of cortical recording. B. summary of firing rate changes across vigilance states in six thalamocortical areas.

mice in total. After spike sorting, we quantified firing rates of each single unit during wake, NREM, and REM sleep. Our analysis revealed that cortical areas show heterogeneous activity patterns and high-order cortical area is as active as during wakefulness, contrary to the concept that the brain is resting during sleep. The results provide new insights for fundamental functions of sleep. (Fig. 4).

(7) Cortical Neural Network Function in Wake and Slow-Wave Sleep (Greene/Vogt Lab)

Transitions between waking and sleep are characterized by profound changes in the neuro-modulatory environment. Both monoaminergic and cholinergic activity is much lower in NREM sleep compared to waking. We have identified a surprising increase in the response of cortical neurons to optogenetic stimulation in mouse cortex - its time-course matches the expected timing of the neuromodulatory changes. The spike integration time window was wider during NREM sleep, a sign of reduced inhibitory circuit activity (Fig. 5). A manuscript on these findings was accepted for publication (Matsumoto *et al.* Sci Rep, 2020). We are now following up on these findings with in-vitro recordings of defined cortical circuits under different neuromodulatory environments.

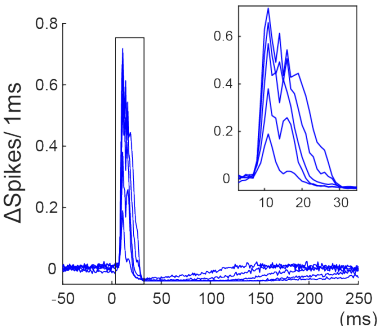


Fig.5. Larger responses are broader - a sign of reduced inhibition

Large ensembles of neurons generate the EEG signals that are essential to the analysis of brain states in waking and sleep. Typically only the frequency domain of these signals is analyzed. We are developing and using novel analytical tools that investigate the stability of these signals over time by determining the coefficient of variation of the envelope (CVE) (Fig. 6). We have found that Sleepy mutant mice show a decrease in stability of several EEG signals, despite higher average signal strength. This loss of signal stability is thus an important additional marker for sleep disturbances. A manuscript is in final preparation.

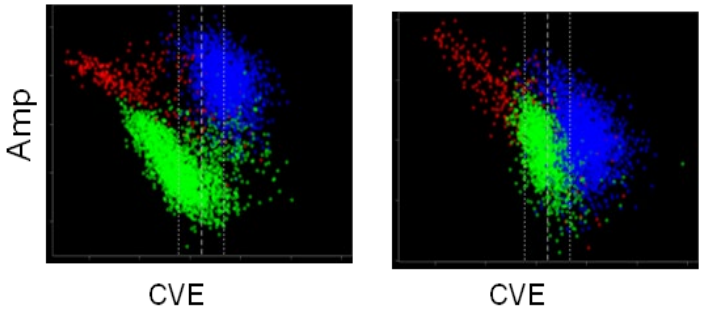


Fig. 6. Normal (left) and Sleepy mutant (right) CVE analysis.

(8) Role of sleep in functional brain regeneration (Sakaguchi Lab)

Separate evidence revealed the function of sleep for regenerative capacity of mammalian brain (Koyanagi *et al.*, Neural Regen Res, 2019) and for memory. For example, we have shown that neurogenesis in the adult- hippocampus, a prominent mechanism of mammalian brain regeneration, plays essential roles for memory. In addition, we have shown that a hippocampus dependent memory can be manipulated during sleep by auditory stimuli using our memory paradigm, which mimics PTSD symptoms. Moreover, we showed a correlation of memory impairments to sleep alterations in Alzheimer's disease model mice (Maezono *et al.*, eNeuro, in printing). Therefore, we examined the function of the adult-born neurons (ABNs) in the hippocampus for memory in naturally sleeping mice using miniaturized endoscope (Srinivasan *et al.*, Biochem Biophys Res Commun, 2019) and optogenetic manipulation (Fig. 7B). We found that the ABNs activated during learning reactivate during REM

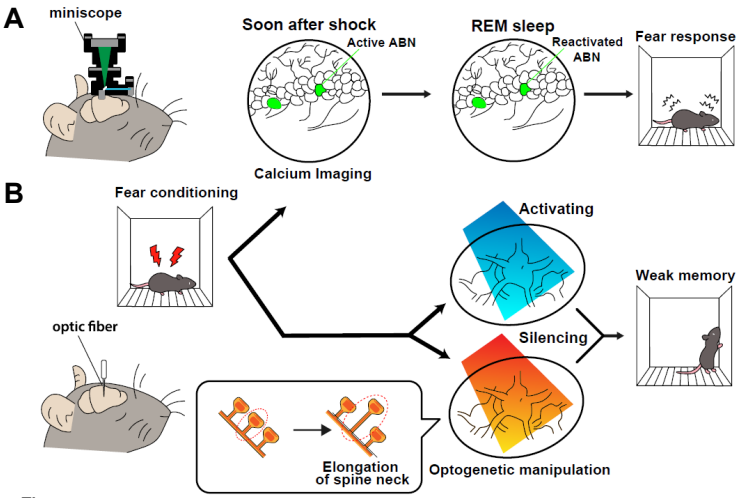


Fig. 7A. Activated ABNs during fear learning reactivate during REM sleep. B. Optogenetic alteration of the ABNs during REM sleep impaired spine structural remodeling and memory consolidation.

sleep and optogenetic alterations of these activities during REM sleep impair fear memory consolidation (Fig. 7A, Kumar *et al.*, Neuron, in printing). These results point towards essential roles of sleep in functional brain regeneration.

(9) Genetic dissection of sleep using Drosophila (Toda Lab)

Hirofumi Toda started his appointment at IIIS since July 2019 in order to establish a new lab to investigate molecular regulation of sleep using *Drosophila* (fruit flies) as a genetic model system. After his appointment, he immediately went back to his previous lab at University of Pennsylvania/HHMI to finish up his on-going project for three months, while he wrapped up a project of identifying a role of a novel gene that regulates sleep in *Drosophila*. This project is currently prepared for submission to a scientific journal. After his brief staying at US, he launched his own lab at IIIS in October 2019. Since then, he prepared all the essential equipments for molecular biology, *Drosophila* genetics and behavior to measure sleep in Drosophila. In addition, his lab houses a behavior assay room, in which the temperature and humidity can be precisely controlled for fly behavior assays including locomotion, courtship and learning/memory.

In 2020, he will complete his lab setup to run all the necessary experiments for molecular biology, Drosophila genetics and fly sleep behavior measurements. His research focus on a specific gene, '*nemuri*' that he originally found through a genome-wide, non-biased gain-of-function behavior screen. Nemuri is an anti-microbial peptide and gets expressed upon infection to induce sleep. He will investigate the molecular cascade of how *nemuri* signal through to finally induce sleep in *Drosophila* through genetic and neuronal screen. In addition, with a close collaboration of biochemist, he will try to identify the molecular binding partners of Nemuri to decipher the molecular function of Nemuri in cells. Through a series of experiments, he hopes to understand the molecular link between sleep and immunity (Toda *et al.*, Science, 2019).

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.

To elucidate pathogenesis of sleep disorder, we have also expanded human physiological studies of sleep, since the inauguration of Human Sleep Lab in April 2019. We aim at developing translational studies by bridging between mouse model studies and human physiological/ pathogenesis studies.

(1) Studies to understand the molecular/neural basis of sleep disorders. (Liu/Sakurai Lab)

CDKL5 deficiency disorder (CDD) is a devastating X-linked neurodevelopmental disorder caused by pathogenic mutations in the cyclin-dependent kinase-like 5 (Cdkl5) gene. The majority of CDD patients display severe sleep problems. We characterized baseline sleep/wake patterns and recovery sleep following sleep deprivation in adult Cdkl5 knockout male mice. Cdkl5 null mice exhibited increased sleep latency, reduced sleep time, shorter sleep episode duration, and frequent awakenings compared to WT mice (Cao *et al.*, unpublished). Our results suggest that the Cdkl5 knockout mouse model may be a useful genetic model for studying sleep disruptions in CDD patients.

Sleep disturbances have long been recognized as a core symptom of post-traumatic stress disorders (PTSD). The neural basis of traumatic stress-induced sleep abnormalities remains poorly understood. Here we found that a single prolonged stress (SPS) could induce acute changes in sleep/wake duration and electroencephalogram (EEG) power spectrum, as well as long-term EEG alterations (Fig. 8). The medial prefrontal cortex (mPFC) showed persistent activity during and after traumatic stress. Chemogenetic inhibition of mPFC during SPS could specifically reverse the SPS-induced acute suppression of the delta power (1-4Hz EEG)-a measurement of sleep quality-of non-rapid-eye-movement sleep (NREMS), but also abrogate long-term EEG abnormalities. Together, these findings establish a mechanistic link between hyper-activation of mPFC and traumatic stress-induced sleep-wake EEG disturbances (Lou *et al.*, submitted).

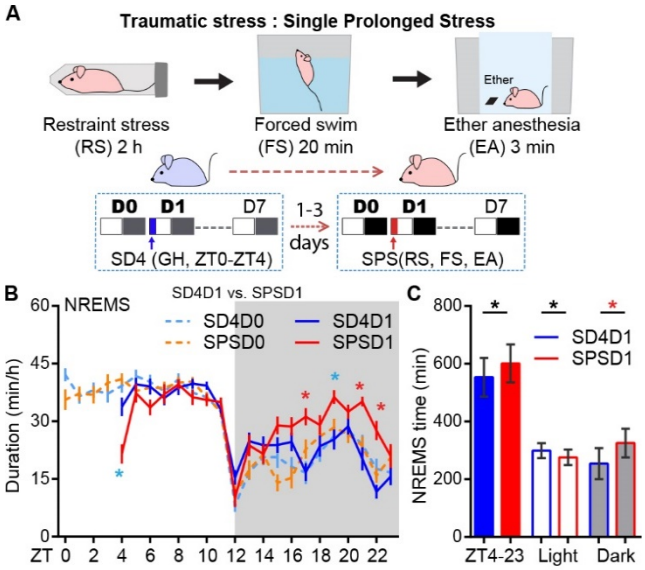


Fig. 8. Single prolonged stress affects sleep/wake architecture.
A. Experimental design for sleep/wakefulness behaviors analysis of traumatic stress model: single prolonged stress (SPS, ZT0-ZT4) vs. gentle handling (SD4, ZT0-ZT4). EEG/EMG was continually recorded during the whole experimental session in mouse home cage. Changes in sleep-wake duration, absolute and relative EEG power density were compared for the same animals. B, C. Analysis of circadian (B) and total time (C)of NREMS, REMS and wake states of wild-type mice (n = 20) on the day with SD4 or with SPS treatment (SD4D1 and SPSD1), and also on the previous day accordingly (SD4D0 and SPSD0). *(black) P < 0.05; *(cyan) P < 0.01; *(red) P < 0.001; ns, P > 0.05.

(2) A novel neural circuit of innate fear-associated hypothermia. (Liu/Sakurai Lab)

Fear is a fundamental emotion accompanied by appropriate defensive behaviors and physiological responses to enhance survival under dangerous circumstances. For example, freezing has been recognized as a typical defensive behavior in predator-evoked innate fear condition. Additionally, some prey animals show a significant change in body temperature as a defensive strategy for survival when encountering their predators. However, the neural basis of thermoregulation under innate fear condition is still unclear. Here, we found 2-methyl-2-thiazoline (2MT), an analog of predator odor TMT (2,4,5-trimethyl-3-thiazoline), induces potent freezing and hypothermia in mice. We identified that the transient receptor potential ion channel A1 (Trpa1) was essential for 2MT-evoked freezing and hypothermia. Our studies revealed that the external parabrachial nucleus (PBel) and their input to the parasubthalamic nucleus (PSTh) contribute to 2MT-induced hypothermia (Fig. 9). Optogenetic activation of 2MT-induced Fos-expressing neurons in PBel, and their axon terminals in PSTh using CANE (Capturing Activated Neuronal Ensembles) system, which allows us to specifically label and manipulate activated neural population, induced both freezing and hypothermia in mice. Conversely, inhibition of Vglut2 positive neurons in PBel and PSTh with the chemogenetic DREADD system attenuated 2MT-induced freezing and hypothermia. Moreover, we found that PSTh neurons project to the nucleus of the solitary tract (NST) to mediate 2MT-induced hypothermia (Fig. 9). Optogenetic activation of NST projecting neurons in PSTh induced hypothermia but not freezing, suggesting the existence of another efferent brain region from PSTh to trigger freezing. In conclusion, we identified a novel brain circuit regulating predator odor induced freezing and hypothermia responses (Liu et al., unpublished).

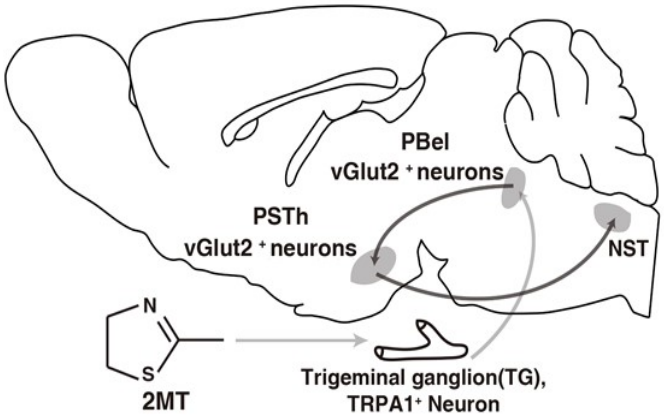


Fig. 9. Novel neural circuits regulating innate fear induced hypothermia

(3) Neural basis of orgasm and pain resistance in mice. (Liu/Sakurai Lab)

The biological purpose of sex is for reproduction or the transfer of genes to the next generation. In other words, the desire for sex is the desire for future life. We expect that the desire for sex may be fulfilled by achieving the "orgasm". In the case of a male mouse, sex consists of a series of sequential behaviors: female recognition, chasing, mounting, intromission, and ejaculation as the climax. It is often thought that ejaculation triggers orgasm or vice versa. However, the neural representation and the physiological features of orgasm remain unclear. We discovered that male mice fell down and was immobilized for about 20 seconds immediately after ejaculation. We suspect that this ejaculation induced tonic immobility state would be the orgasm-like state (Fig.10). To understand the neural representation of this orgasm-like state, we applied in vivo imaging with the fiber photometry system, electroencephalogram (EEG) recording, and in situ hybridization based histological analysis. Before the orgasm-like state, we observed the drastic surge of neural activities in VTA dopaminergic neurons. The EEG power spectra analysis showed that the theta power became dominant during the orgasm-like state. The CAT-FISH (cellular compartment analysis of temporal activity by fluorescence in situ hybridization) of Fos, an immediately early gene that reflects neural activities, revealed that several neural populations seem to be activated during this orgasm-like state. Moreover, we found that the pain response is suppressed during the orgasm-like state. The recording of neural activities with fiber photometry revealed that the neural activities in the thalamus, a central relay station of pain information, were suppressed during the orgasm-like state. Taken together, these results suggest that the orgasm-like state in male mouse may be defined by the tonic immobility state after ejaculation, drastic surge of neural activities in VTA dopaminergic neurons, EEG theta power, and pain insensitivity (Miyasaka *et al.*, unpublished). We are now trying to understand the neural mechanisms of the pain suppression during the orgasm-like state.

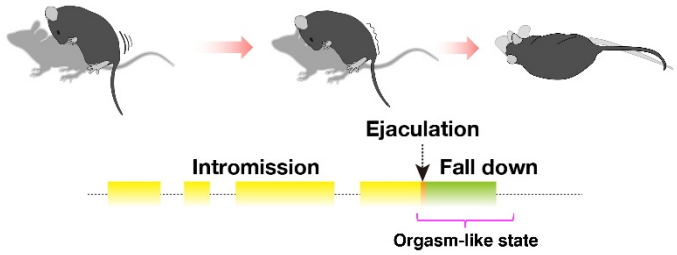


Fig. 10. Male mouse sexual behaviors.

(4) Detailed description of energy metabolism during human sleep (Satoh/Tokuyama Lab)

The present study measured sleeping metabolic rate using a whole-room indirect calorimetry. By adopting an online magnetic sector mass-spectrometer for gas analysis the first time in the world, and developing a new algorithm for improved transient response, time resolution of our whole-room indirect calorimetry in IIIS is currently the best in the world. State-of-the-art whole-room indirect calorimetry made it possible to de scribe characteristic phenotype of energy metabolism (Ogata, *et al.*, Am J Clin Nutr, 2019). Human sleep is consolidated into a single prolonged period, and its metabolic consequence is to impose an extended period of fasting. It has been assumed that oxidized substrate shift from carbohydrate to fat during the sleeping period. Contrary to this presumption, our study revealed dynamic characteristics of sleeping energy metabolism; energy expenditure and carbohydrate oxidation clearly begin to increase

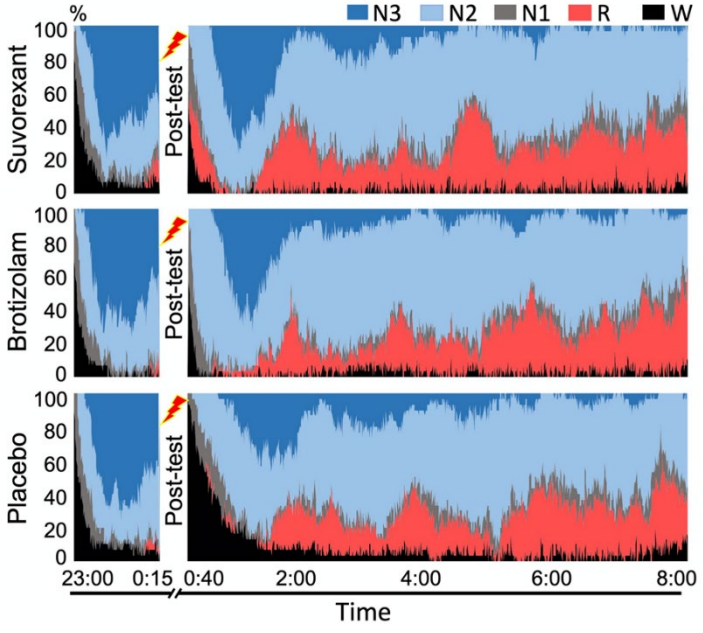


Fig. 11. Cumulative display of sleep architecture in all 30 subjects. The percentage of subjects in each sleep stage is shown. The subjects were forced awake at 00:15 and went back to sleep at 00:40.

prior to awakening (Kayaba, *et al.*, Metabolism, 2017). The mechanism and physiological significance of our findings remain obscure, but our ongoing study following the present study revealed sexual dimorphism in time course of sleeping energy metabolism; the increase in carbohydrate oxidation begins 2~4 h earlier in females compared to males (Zhang, *et al.*, Physiol Rep, 2020). Fuel selection in the body is estimated from respiratory quotient (RQ), i.e., the ratio of CO_2 production to O_2 consumption. Higher RQ implies dominant carbohydrate oxidation and lower RQ reflects fat oxidation. Compared to daytime, sexual dimorphism and individual differences in RQ become significant during sleep. Because of absence of masking effects such as postural changes, physical activity, ambient temperature and meals, indirect calorimetry during sleep may provide a window to get insight into individual metabolic state.

Regulatory mechanisms of sleep and energy metabolism share common molecules such as orexin, insulin, etc. Orexin receptor antagonist improved sleep efficiency, increased REM sleep and suppressed energy expenditure during sleep (Fig. 11) (Seol, *et al.*, Proc Natl Acad Sci USA, 2019). In this experiment, side-effect profile of an orexin receptor antagonist (suvolexant) and γ-aminobutyric acid A receptor agonist (brotizolam) on physical/cognitive functions upon forced awakening was evaluated. Although brotizolam significantly impaired the overall physical/cognitive performance compared with placebo upon forced awakening, there was no significant difference in the total z score of performance between suvolexant and placebo. When the subjects were allowed to go back to sleep after the forced awakening, the sleep latency was shorter under the influence of hypnotic agents (~2 min) compared to the placebo trial (24 min), and the rapid eye movement latency was significantly shorter under orexin receptor antagonist (98.8, 81.7, and 48.8 min for placebo, brotizolam, and suvolexant, respectively).

(5) Understanding how sleep and sleepiness relate to the human mind and behavior (Abe Lab)

Our laboratory aims to understand how sleep and sleepiness interact with the human mind and behavior. We have achieved three findings during this fiscal year. (1) One of our goals is to understand the psychological function of human REM sleep. Our recent study investigated the effects of odor stimulation on dreaming during REM sleep (Fig. 12A) (Okabe *et al.*, Sleep Med, 2020). We found that people more familiar with the smell of phenylethyl alcohol (PEA; a rose-like odor) reported more unpleasant dreams after the stimulation of that odor during REM sleep than those less familiar with it (Fig. 12B). This effect might be explained by the fact that familiar odors tend to be perceived more strongly, and the amygdala, which has a direct connection with the olfactory pathway and is primarily involved in processing negative emotions, is activated more strongly after the stimulation of familiar odors during REM sleep. We previously found a novel brain potential whose current sources were estimated in the emotional brain regions (e.g., Abe *et al.*, Clin Neurophysiol, 2008). Using odor stimulation and novel brain potential, we will investigate how emotions occur in dreaming and what the functions of emotion are during REM sleep. (2) We are also investigating how daytime activity affects sleep and vigilant attention. In a previous study, we showed that high cognitive workload enhances arousal during wakefulness and promotes sleep homeostatic response during sleep (Goel *et al.*, Sleep, 2014). In collaboration with JAXA, we also found that a 15-minute daily aerobike exercise increases sleep duration and improves daytime vigilant attention during 2-week isolation in a closed environment (Ohira *et al.*, submitted). We will examine the effect of exercise on sleep and vigilant attention in more detail using our highly controlled human sleep laboratory. (3) It is well known that sleep loss causes fluctuations in response times. This phenomenon is called "state instability." We are conducting studies to elucidate the characteristics of state

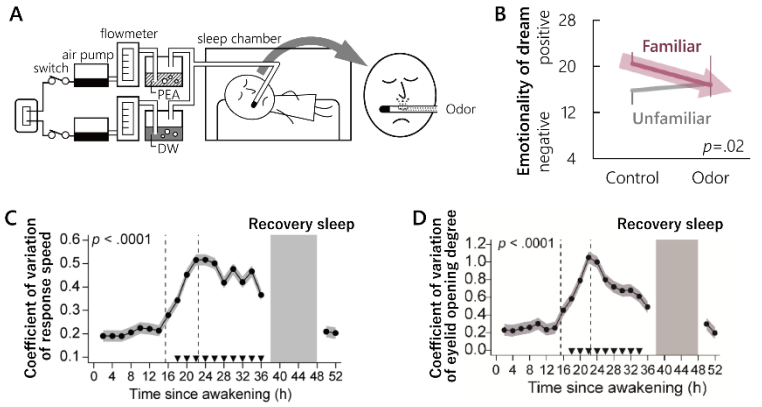


Fig. 12 (A) Olfactory stimulation device. (B) Familiar odor induces negative dream. (C) Wake state instability of sustained attention during a 38-hour sleep deprivation experiment. (D) Wake state instability also occurs in the eyelid opening degree.

instability and the neural and physiological basis of this phenomenon. We found that the wake state instability of vigilant attention (Fig. 12C) also occurs in the degree of eyelid opening (Fig. 12D) (Abe *et al.*, Sleep, 2020). Using this index may enable us to estimate vigilant attention without conducting vigilance tasks. In fact, we developed a novel method for detecting multilevel vigilant attention by integrating this marker with other eye-related indices (Abe *et al.*, Sleep, 2020). We will conduct research to find practical applications of this method.

(6) Orexin levels with Alzheimer's disease and DLBD (Kanbayashi Lab)

It is well known that sleep disorders increase with age, but sleep disorders are often seen, especially in patients with these Alzheimer's dementia and diffuse Lewy body disease (DLBD).

From recent research progress, the onset of dementia and sleep disorders are not merely a one-way relationship, and it is possible that sleep abnormalities may contribute to the onset of dementia and its subsequent deterioration. We measured CSF orexin levels of the patients with AD and compared to mini mental state examination (MMSE) (Fig. 13).

The association between cognitive function and orexin levels were not observed in DLBD, compared to AD. While in DLBD, patients who had enough amount of orexin had a more severe RBD symptom (Fig. 14).

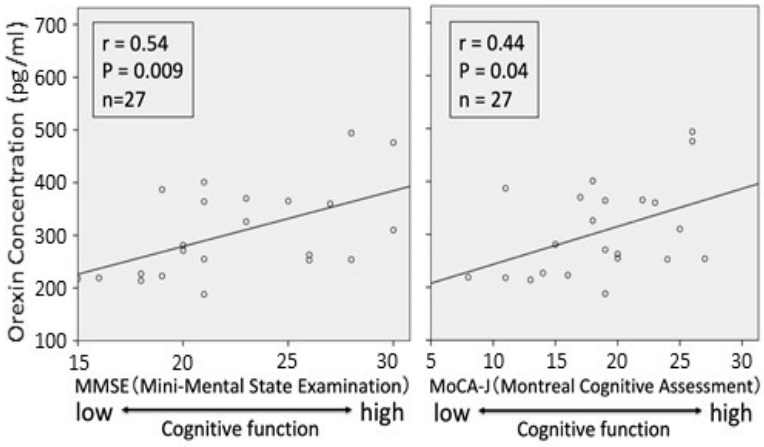


Fig. 13. The positive association between cognitive function and orexin levels was found using MMSE and MoCA-J in AD patients. The patients who had higher amount of orexin had better cognitive function (Shimizu, et al., J Alzheimers Dis 2020).

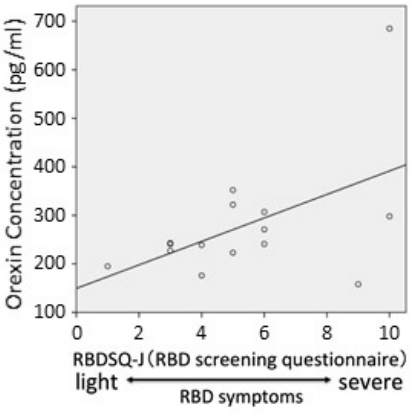


Fig. 14. Patients who had enough amount of orexin would not transit to REM sleep easily, they often became incomplete REM sleep, RBD. In other words, patients who had low amount of orexin would easily transit to REM sleep (Shimizu submitting).

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

We are discovering lead compounds of novel drugs modulating sleep/wakefulness 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.

(1) Design and synthesis of orexin receptor ligands (Nagase/Kutsumura and Yanagisawa/Funato Lab)

The non-peptidic small molecules showing agonist activity for orexin receptors (OXRs), especially for OX_2R, have been expected as a chemotherapeutic agent for narcolepsy. Nagase's group have discovered the potent OX_2R selective agonists YNT-185 (EC_{50} = 28 nM; selectivity ratio to OX_1R >100 times) and YNT-1757 (EC_{50} = 0.6 nM; selectivity ratio to OX_1R >1000 times) confirmed its anti-narcoleptic effects in the murine narcoleptic model. In the course of research on OX_2R selective

agonists, Nagase's group discovered that a novel compound having a unique mother skeleton "Trimer compound" showed OX_1R selective antagonistic activity. With the aim of creating OXRs agonists, they began a major transformation of the mother skeleton by removing the moiety "accessory site" that contributes to the antagonistic activity of the Trimer compound, based on their own experience. As a result, Nagase's group have synthesized a novel OXRs agonist X, having tetralin skeleton (EC_{50} = 30.7 nM for OX_1R, EC_{50} = 2.03 nM for OX_2R, Japanese Patent 2019-180842). In addition, as a result of further derivatization of this tetralin compound X, the following four first OXR ligands were successfully synthesized. That is, (i) OX_2R selective agonist A (EC_{50} = 0.69 nM for OX_2R) as a tetralin derivative, (ii) dual OXRs agonist B (EC_{50} = 3.73 nM for OX_1R, EC_{50} = 0.92 nM for OX_2R), (iii) OX_1R selective agonist C (EC_{50} = 1.86 μM for OX_1R), and (iv) OX_1R selective antagonist D as a tetralin derivative (IC_{50} = 43.8 nM for OX_1R) were synthesized (Japanese Patent 2019-180842). In near future, through studies on the structural optimization of these tetralin derivatives, Nagase's group plan to lead to the development of improved OX_2R selective agonist of YNT-1757, first OX_1R selective agonist, and so on.

On the other hand, Nagase's group have also continued to develop OX_1R specific antagonist with morphinan skeleton. This research project does not directly lead to the development of a chemotherapeutic agent for narcolepsy. However, to elucidate the functions and roles of OXRs *in vivo* in detail, it is important to develop OXRs specific (perfectly selective) ligands. In the research background, Nagase's group reported that the morphinan compounds YNT-707 and YNT-1310 show potent and extremely high selective antagonistic activity against OX_1R in 2017 (Nagase *et al.*, J Med Chem, 2017). In 2019, the study for the essential structure for the expression of OX_1R antagonistic activity of YNT-707 was conducted. The structure-activity relationship studies for the 14-hydroxy group, the 3-methoxy group, the D-ring, and the substituents on the 17-nitrogen in the morphinan YNT-707 were carried out to achieve important information about interactions between OX_1R and morphinan ligands (Saitoh *et al.*, Bioorg Med Chem Lett, 2019; Saitoh *et al.*, Bioorg Med Chem Lett, 2019; Saitoh *et al.*, Bioorg Med Chem Lett, 2020). Based on the findings and information, Nagase's group will develop structurally simpler novel scaffolds to show OX_1R antagonistic activity, instead of the expensive morphinan-type ligands.

(2) Development of an EEG-measuring wearable device and software for in-home sleep staging (Yanagisawa/Funato Lab and Abe Lab)

We have conducted the study of "Development of the sleep measurement service for people suffered from sleep problems all over the world" as one of projects of the Regional Innovation Ecosystem Program of MEXT since FY 2017. In the project, 3 groups, i.e., 1) IIIS, 2) Center for Computational Science, University of Tsukuba (CCS), and 3) S'UIMIN Inc., a spin-out venture of IIIS established in October 2017, collaborate to develop an EEG-measuring-wearable device and algorithms/software based on the artificial intelligence for fully-automated sleep staging.

In FY 2019, the team succeeded in developing a prototype of the wearable device (Ver. 1.5). Initially, the headband-type wearable device developed by NeuroSky, had several problems including high non-score (NS) rates due to noises/baseline drifting caused by sweating, detachment of electrodes or high contact resistance (impedance) of the electrodes. In addition, the pain problem due to tightening of the headband was unavoidable although several improved designs were examined. We solved these problems by changing the design to the separate-electrode-type, in which electrodes were separated from the device body so that it was installed at the bedside. The simultaneous measurement between the device and the conventional electroencephalograph (PSG) showed an NS rate of 0.0%, a concordance rate of 93.5% and a κ coefficient of 0.90, achieving the highest ever accuracy. The first pilot study using the device (Ver. 1.5) was performed from November to December 2019. This clinical research was approved by the IRB of University of Tsukuba Hospital, and was conducted in collaboration with IIIS, S'UIMIN Inc. and CMIC Healthcare Institute Co., Ltd. A sleep measurement was conducted on 107 healthy subjects for consecutive 7 nights and more than 95% of subjects were able to acquire EEG data, total of 702 nights. We are further developing the device (Ver. 2.0) to start a sleep measuring service in FY 2020.

CCS team has been developing automated sleep stage scoring software based on a deep learning model. They started from studies of sleep stage scoring for mice and have developed a few algorisms. The newest one was "MC-SleepNet", which combines two types of deep neural networks. The evaluation of its performance using a large-scale dataset that contains 4,200 records of EEG and EMG of mice revealed that MC-SleepNet could automatically score sleep stages with an accuracy of 96.6% and κ index of 0.94 (Yamabe *et al.*, Sci Rep, 2019).

They are developing an automated staging software for the wearable device, which consists of two modules, feature extraction, and scoring modules. The feature extraction modules extract the features, such as characteristic waves, from measured EEG and EOG signals, and the scoring module learns the relationship between the features and the sleep stages scored by human experts (training data). In the development, we focused on designing the feature extraction modules. For example, we employed two convolutional neural networks (CNNs) in parallel to extract features. The measured EEG signals are often contaminated by EOG, due to the position of electrodes. Although these EOG signals are "noises," they can improve the scoring accuracy if we consider them properly. To use both of EEG and EOG signals effectively, we used two CNNs specialized for EEG and EOG features, respectively. The experiments using the 702 sleep records and corresponding training data showed that our model achieved the agreement rate with human experts of more than 80%. Although there are some rooms for improvement, we will be able to use the software for clinical purposes soon.

1-1-4. Hibernation

The new finding of the function of a group of neurons (Q neurons) in hypothalamus inducing regulated hypometabolic state has opened a door to study mechanisms of hibernation regulation.

(1) A novel neuronal pathway that induces hibernation-like hypometabolic states (Sakurai/Hirano Lab)

Hibernating mammals actively lower their body temperature to reduce energy expenditure when facing food scarcity. Because a hypometabolic state could benefit many medical applications, this ability has evoked great interest. We found a hypothalamic neurons that induces a long-lasting hypothermic/hypometabolic state similar to hibernation (Q neurons) (Fig. 15). In this state, QIH, although body temperature and O2 consumption are maintained very low, the ability to regulate metabolism still remains functional as in hibernation. No obvious tissue/organ damage nor abnormalities in behavior were observed after recovery. This finding opens the door to the development of the induction of a hibernation-like state, which would have potential applications in non-hibernating mammalian species, including humans (Takahashi *et al.,* Nature, in press).

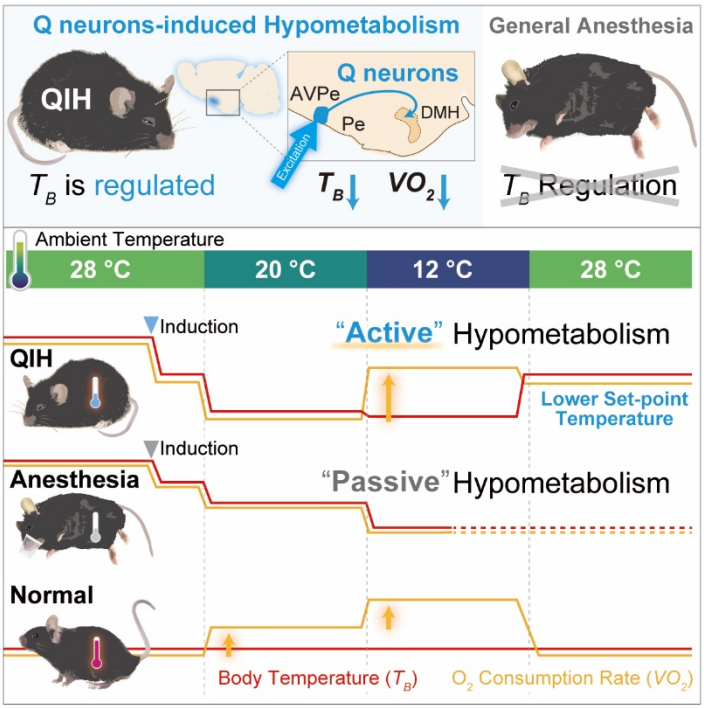


Fig.15. during QIH mice are able to adopt their bodily functions and behavior in response to change in ambient temperature.

1-2. Research environment including facilities and equipment

The development of the facilities has been continuously moving forward.

For further expansion of the experimental medicine in IIIS, we newly established a facility for human sleep research, Human Sleep Lab in Innovation Medical Research Institute (COI Building) located in Kasuga Campus of the university. This 211 m^2 wide facility near Tsukuba Station has 4 beds of sleep measurement chambers, a bath room, a monitoring room, and 1 bed of a human calorimeter chamber (for whole-room indirect calorimetry during sleep), which was moved from the IIIS Building. It allows sleep measurement of multiple subjects (up to 5) in parallel and improves efficiency of our human sleep research significantly. It also enables us to conduct intervention tests such as the constant routine protocol. Since the establishment of Human Sleep Lab, nearly 300 sleep measurements have been conducted in the lab and human sleep data have been collected. Further analysis of these data could accelerate our studies on experimental medicine.

Another significant development is the completion of Mobile Sleep Lab, a sleep experiment facility mounted on vehicle. We converted a fuel cell bus, SORA donated by Toyota Motor Corporation into

Mobile Sleep Lab in the collaboration with F-MIRAI, R&D Center for Frontiers of MIRAI in Policy and Technology, which is a R&D center in University of Tsukuba established by the university and Toyota. In Mobile Sleep Lab (the fuel cell bus), there are 2 beds of sleep measurement chambers, a monitoring room, a bath room and a wash sink. This makes it possible for a sleep experiment facility itself to become transferable and eliminate location constrains for accurate sleep measurement such as polysomnography. It is expected to be a device that can drastically change both aspects of basic sleep research and clinical sleep research in the future.

For further expansion of neuroscience study in IIIS, we invited a new PI, who studies molecular genetics of sleep using fruit flies (*Drosophila*). We have set up a new fly lab with all the equipment necessary for the sleep research using flies, including a dark chamber with a precise air-conditioning system to keep temperature and humidity, over a hundred of Drosophila Activity Monitors (DAM) system, dozens of incubators for fly cultures, and a fully functional biology lab for fly manipulations with molecular biological techniques. With such systems, a full range of sleep studies using *Drosophila* such as non-biased genetic screens can be performed.

1-3. Competitive and other funding

Since most of the PIs in the core group of IIIS were invited from the outside of University of Tsukuba, very limited competitive funding was available in its launch, except for Yanagisawa's grant of the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST), which started before the inauguration of IIIS. As IIIS grows rapidly, great efforts to raise competitive funding have been made and it has drastically increased, as shown in Fig. 16. The total amount of the funds executed each year had grown from ¥1.5 M in FY 2012 to ¥770 M in FY 2018, more than 500 times. In FY 2019, we succeeded in increasing it further by 5%, and it reached ¥808 M. Particularly, the funding of research collaboration projects significantly increased from ¥107 M (FY 2018) to ¥213 M (FY 2019).

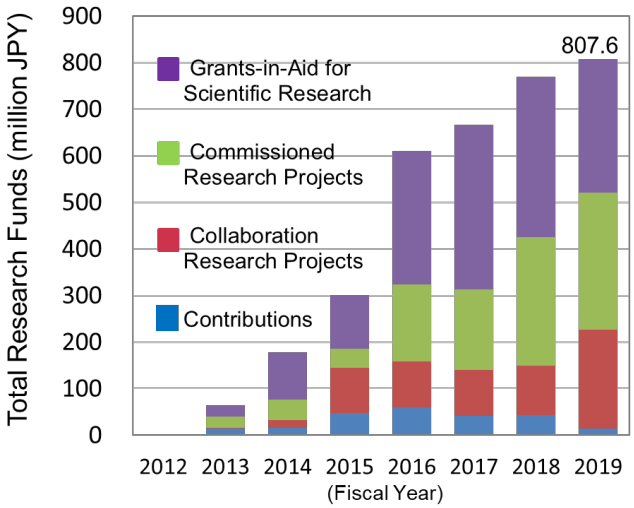


Fig.16. Rapid growth of the competitive funding executed in each year

IIIS would be assessed as a world-top level institute in this aspect as well. We continue the efforts to secure the same or even higher levels of external research funds after FY 2019.

1-4. State of joint research

Efforts have been continued to increase and expand collaboration/research alliances especially in the field of translational research with outside groups including groups in University of Tsukuba, the Satellites, and external research institutions.

(1) Akita University Graduate School of Medicine (Domestic Satellite)

After concluding the collaborative research agreement with the new Satellite PI, Kazuo Mishima, in October 2018, we started the first collaboration with him on a pilot study of the sleep measurement at home by using a wearable EEG device developed by S'UIMIN Inc. As reference data to be compared with the objective sleep measurement based on EEG, self-assessment (subjective evaluation) for sleep quality/quantity and information on sleeping habits would be very useful for diagnosis. To obtain these information, he offered the algorithm of self-checking sleep disorders developed by his team in the previous position, National Center of Neurology and Psychiatry. The algorithm of the self-assessment was successfully adopted in the pilot study of the sleep measurement at home with the wearable EEG device in which 104 volunteers participated to conduct the measurement for 7 consecutive nights.

A kick-off meeting of the collaboration with him was unfortunately postponed twice due to conflicts with his busy schedule, but it was held at last on November 28, 2019 in IIIS, where he gave a talk at the IIIS seminar and we discussed plans of further collaborations. We expect fruitful collaboration with him on the translational research in future.

(2) Ibaraki Prefecture/Ibaraki Prefectural Medical Center of Psychiatry (Domestic Satellite)

Since FY 2015, we have conducted a joint project with the Hospital Management Division of Ibaraki Prefecture to promote clinical research of sleep disorders in IIIS and to establish a sleep medical center in Ibaraki Prefectural Medical Center of Psychiatry. We, however, found it very difficult to recruit good medical specialists in sleep medicine. Fortunately, at the end of FY 2018 we succeeded in finding 2 specialists, Takashi Kanbayashi in Akita University Graduate School of Medicine and Hideaki Kondo in Faculty of Medical Science Kyushu University. Kanbayashi was appointed to PI in IIIS as well as the Director at Ibaraki Prefectural Medical Center of Psychiatry as of April 1, 2019. Kondo was appointed as Associate Professor as of April 1, 2019. In FY 2019 they conducted the translational research including the diagnosis and pathophysiological study of hypersomnia patients such as narcolepsy, and the development of the treatment for delayed sleep phase syndrome (DSPS). Many Japanese students are suffered from DSPS and this condition is one of the reason of school refusal. They are also involved in the development of the sleep measurement services and AI software for diagnosis of sleep disorders in collaboration with S'UIMIN Inc.

In April 2020, Kondo will be promoted to Director of Ibaraki Prefectural Sleep Clinic in Mito, Ibaraki. He will leave IIIS but continue the collaboration as a Visiting Professor.

(3) RIKEN Center for Biosystems Dynamics Research

Since December 2017, T. Sakurai has collaborated with Genshiro Sunagawa in Center for Biosystems Dynamics Research, RIKEN on the study of the hypothalamic neurons that induces a long-lasting hypothermic/hypometabolic state similar to hibernation (Q neurons). The collaboration has been formalized by concluding a research collaboration agreement between RIKEN and University of Tsukuba as of April 2019. The first paper reporting this exciting result has been accepted for the publication on Nature. We plan to expand the collaboration to conduct a feasibility study of the synthetic hibernation.

(4) RIKEN Center for Advanced Intelligence Project

In FY2019, we have started another collaboration on the functional analysis of dopamine in the sexual behavior of the male mouse with Jun Seita in Center for Advanced Intelligence Project of RIKEN. We expect that their data analysis using the deep learning will let us understand how dopamine regulate sexual behavior.

1-5. Appraisal by society and scientific organizations

The research achievements of IIIS are highly recognized in and outside Japan, and IIIS researchers have received many prestigious awards. In FY 2019, Yanagisawa received European Narcolepsy Research Award and Takamine Memorial Daiichi Sankyo Prize for his remarkable contribution to the progress and development of medicine through his discovery of orexin and endothelin. Further, he was commended for his contribution to the development of culture and society through the sleep research. In FY 2019 he was designated as Person of Cultural Merit, which is an official Japanese recognition and honor awarded annually to select people who have made outstanding cultural contributions. He also received Ibaraki Prefecture Honor Award honoring his contribution to Ibaraki Prefecture through his sleep research. Other PIs, non-PI faculty, postdocs, and graduate students have also been recognized for their outstanding achievements by various academic organizations as shown in Appendix 1-2.

With regard to invitational lectures, all PIs have been invited as speakers and they have given about 100 lectures at domestic and international conferences in FY 2019. In particular, Yanagisawa and T. Sakurai have done a lot of Keynote/Plenary Lectures as the world-leaders in basic research on sleep. Furthermore, Yanagisawa was appointed to the chairman of the 45th Annual Meeting of Japanese Society of Sleep Research held in September 2020, Yokohama.

All of these reflect high appraisal from research communities and society for IIIS and further boosts domestic and international visibility of IIIS.

1-6. Applications of research results

(1) Patent applications

We filed 3 patent applications as listed in the following table. The applications are all commensurate with the research objectives of IIIS, *i.e.*, to elucidate the sleep/wake regulation mechanism and the pathogenesis of sleep disorders, and to develop new treatment methods. Due to the nature of our research subjects, sleep sciences, the major means of practical application of research results include licensing of patents to pharmaceutical/diagnosis companies. We are engaging in negotiation with multiple companies for licensing.

(2) Joint research with companies

The joint research projects between IIIS and the companies described below aim for practical applications of research results (seeds) obtained at IIIS to solve the problems of sleep disorders. In particular, we focus on translational research such as drug discovery in cooperation with pharmaceutical companies and clinical research of sleep-aiding products in collaboration with companies/research institutions.

Fujifilm Corporation

Since FY 2016, we have been conducting the collaboration to provide them with a compound library established by Nagase.

In addition to this collaboration, we have licensed an orexin 2 receptor agonist, YNT-185 and an orexin 1 receptor antagonist, YNT-1310 as research reagents to FUJIFILM Wako Pure Chemical Corp., the subsidiary of Fujifilm.

Toray Chemical Industries, Ltd

Since FY 2014, we have been performing the ongoing joint research with Toray to study sleep modulating activities of Nalfurafin-related compounds. We discovered a kappa opioid receptor agonist with the morphinan structure, YNT-1612, and Toray estimated its *in vivo* activity under MTA. YNT-1612 was found to show a potent antinociceptive activity without addiction and aversion. The most striking point of YNT-1612 is that it causes no sedation, because even the kappa opioid receptor agonist approved for an antipruritic drug, Narfulafine has the adverse effect of severe sedation. That's why it was not applied for postoperative pain. YNT-1612 is expected to be applied for more indications than Narfulafine. We are negotiating conditions for the licensing with Toray.

Nishikawa Co., Ltd.

In FY 2015 we started the joint research with Nishikawa on the effect of body-pressure dispersion of a mattress on sleep. We found that better body-pressure dispersion improved sleep quality (*Sleep Med Res* 10(2): 1-5, 2019). In this study we realized that a mattress with better body-pressure dispersion might help us to keep the lateral positions for a longer time and reduce durations at the supine position. Another method of decreasing durations at the supine position would be a body pillow.

Obstructive sleep apnea (OSA) is a common sleep disorder that is associated with significant negative health outcomes including cardiovascular disease, daytime sleepiness, and neurocognitive deficits. OSA could be divided into positional and non-positional. In order to treat positional OSA, avoidance of supine sleeping position is recommended, and use of body pillow could suppress positional OSA. We are thus conducting a randomized crossover study on use of body pillow as an intervention to treat positional OSA. The reduced supine position with body pillow may contribute as a simple, cheap and effective solution for the treatment of OSA.

Kyocera Cooperation

Since FY 2018, we have conducted the collaboration with Kyocera Co. This collaboration is planned to continue for three years step by step with enough research funding for clinical studies with normal subjects of development and validation of their device. Nocturnal polysomnographic data were recorded from 45 participants in FY 2019. IIIS has a role to examine the dynamics of heart rate variability and blood flow during sleep. We compared several indices among sleep stages using the conventional frequency analysis. However, we could not detect differences among all sleep stages using this method. We, therefore, examined indices that show differences among sleep stages using non-

linear analysis such as detrended fluctuation analysis (DFA). We found that DFA for the heart rate variability shows differences among all sleep stages except between awake and stage N1. Based on this result, Kyocera is developing a device for estimating sleep stages using blood flow data.

Ezaki Glico Co., Ltd.

From December 2019, we started joint research on effects of extracts from citrus fruits on sleep architecture, thermoregulation and energy expenditure during sleep. The citrus extracts are known to stimulate heat dissipation from peripheral skin. We are thus conducting a study based on a working hypothesis that "if dietary ingredient compounds are consumed at the right time of the day prior to the bed time, it would facilitate heat dissipation and decrease core body temperature." Heat loss, indirectly measured by the distal-proximal skin temperature gradient, is the best predictor variable for sleep onset latency. Our projects look for the effective food ingredients to stimulate this process to improve sleep quality.

S'UIMIN Inc.

In October 2017, S'UIMIN Inc. was established as a spin-out venture of IIIS. From FY 2018 to 2019, we performed the collaboration on the research and development of the system of sleep measurement at home. In October 2019, we started the new joint research with S'UIMIN and Center for Computational Science, University of Tsukuba to develop an automated sleep stage scoring software based on a deep learning model. The deep leaning model is to be built by using as training data results of manual sleep staging of wearable EEG device data by skilled clinical technologists. We also plan to develop an automated software for assessment of sleep/diagnosis of sleep disorders based on deep learning model in future.

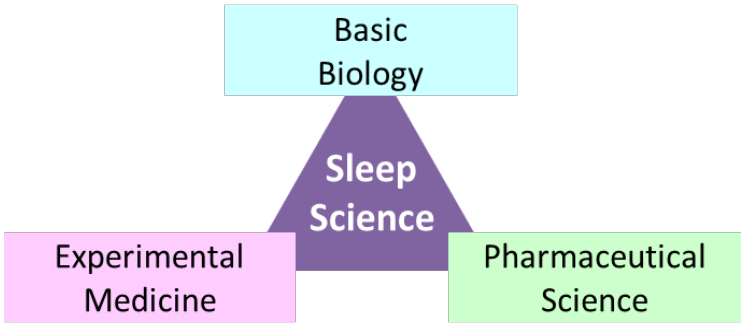
2. Generating Fused Disciplines

* Describe the content of measures taken by the center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields. If any, describe the interdisciplinary research/fused discipline that have resulted from your efforts to generate fused disciplines. You may refer to the research results described concretely in "1. Advancing Research of the Highest Global Level."

2-1. State of strategic (or "top-down") undertakings toward creating new interdisciplinary domains

The initial research objectives we aim to achieve are: 1) to elucidate the fundamental mechanisms of sleep/wake regulation, 2) to elucidate molecular pathogenesis of sleep disorders and related diseases, and 3) to developing and verify treatment strategies for sleep disorders, as discussed 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.

A crucial driving force to create "sleep science" remains the leadership of the Center Director, Yanagisawa, 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.



2-2. State of "bottom-up" undertakings from the center's researchers toward creating new interdisciplinary domains

Collaborative research among labs in IIIS is crucial to fuse 3 research fields into "sleep science." The internal collaborations are becoming more active recently, owing to physically and psychologically open atmosphere created/enhanced by 2 factors, i.e., the open structure of the IIIS Building

and the open communication through unique meetings such as the Work in Progress (WIP) meeting, the Dojo journal club, and B&B.

The labs and offices in IIIS Building are designed as open-labs and open-offices to be shared by a few PIs' groups. Further, the open-office on each floor is connected with a spiral staircase in the stairwell spanning 1st through 4th floor. The open structure makes the physical distance, as well as the psychological distance, of the scientists closer.

Holding the Work in Progress (WIP) meetings and Dojo journal club every week alternately, where all of IIIS member get together at the auditorium and introduce progress of own research and published papers, facilitates open communication among labs. 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. In FY 2019, we also continued more informal meeting organized by one or two labs on-duty, *i.e.*, Brie & Bordeaux (B&B) to help open communication and foster exchanges of ideas. We had B&B five times this year, enjoying casual talks with snacks and drinks in the lounge of IIIS Building.

We hosted 20 WPI-IIIS Seminars in FY 2019, where we invited domestic and foreign researchers in sleep/neuroscience fields almost every other week. Consequently, 166 seminars have been conducted since the inauguration in December 2012. The seminar is open and, in addition to IIIS members, many researchers/students in relevant fields in the university and other public/for-profit organizations participate in the seminar. Every speaker is given the opportunity of individual interviews with all PIs, and the seminars give us opportunities of exchanging research ideas with a broad range of researchers and expanding human networks.

2-3. Results of research in fused research fields

IIIS has reported many successful examples of a) discovery of lead compound, b) concept validation with the lead, and c) optimization of the lead, aiming to development of drugs for i) narcolepsy, ii) insomnia, iii) PTSD, and iv) anxiety disorder.

In these studies, neuroscience labs were in charge of identifying molecular targets suitable for treatment of given diseases (indications), *e.g.*, orexin 2 receptor (OX_2R), orexin 1 receptor (OX_1R) or adenosine A_{2A} receptor. Then the pharmacology labs conducted high throughput screening to find hit compounds showing agonist, antagonist or positive/negative allosteric modulator activity. Among hit compounds, the most promising compound with good activity and favorable chemical characteristics was selected, and then the medicinal chemistry lab synthesized many derivatives of the selected compound. The pharmacology and medicinal chemistry labs closely collaborated to confirm structure-activity-relationship and to find a better compound showing an *in vivo* activity with animal disease models, which would be regarded as a lead compound.

Alternatively, the medicinal chemistry lab developed a lead compound showing agonist or antagonist activity against a receptor whose pathogenic contribution in disease was not clearly elucidated yet, *e.g.*, OX_1R. Then the pharmacology lab used the lead as a chemical probe to study it for the concept validation.

In FY 2019 we published interesting results of a translational (TR) study by the collaboration between neuroscience/pharmacology labs and human sleep physiology labs. The TR study compared effects of an orexin receptor antagonist (suvorexant) and a $GABA_A$ agonist (brotizolam) on human physical and cognitive functions. In animal studies, motor functions were impaired by $GABA_A$ agonists in a dose-dependent manner, while motor coordination was not affected by the orexin receptor antagonist. Double-blind, randomized, placebo-controlled, crossover study with 30 healthy male subjects, compared with brotizolam at equally effective sleep-promoting doses, it was found that suvorexant had an improved side-effect profile when evaluated 90 min after ingestion; score of static balance and sum of z-score of physical and cognitive function test was higher under suvorexant than that under brotizolam.

The second example of TR studies, in which human sleep physiology labs are involved, is the development of a system for sleep measuring at home. For Regional Innovation Ecosystem Program implemented by MEXT, the 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 in November 2016 to start 2 R&D projects aiming commercialization. One of the R&D projects was the development of the sleep

measuring system. In FY 2017, the team succeeded in developing a prototype of the wearable device with 3 channels of EEG and a software for automated sleep staging of polysomnography (PSG) data based on a deep learning model. This achievement let us launch a spin-out venture of IIIS, S'UIMIN Inc. in October 2017 and raise the fund of ¥700 M in capital from Mirai Creation Fund operated by SPARX Asset Management Co., Ltd. in November 2018. In FY 2019, the second prototype of the wearable device, version 1.5 was developed by NeuroSky Co., and the automated sleep staging software was improved to show a consistency as high as 88.1% (κ coefficient of 0.83) with the manual sleep staging of PSG data by skilled clinical technologist. We thus conducted the first pilot study of the sleep measurement at home using the wearable EEG device was performed in November 2019.

The third example of TR studies is collaboration with R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI). We started the collaboration from October 2018, and we have developed Mobile Sleep Lab by remodeling a fuel cell bus lent from Toyota Motor Corporation in FY 2019, as described 1-2. We are starting a validation study to confirm quality of the sleep measurement with PSG equipment in Mobile Sleep Lab.

3. Realizing an 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 (in Appendix 2); exchanges with overseas entities (in Appendix 4); number and state of visiting researchers (in Appendix 5)
- 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. Overseas satellites and other cooperative organizations

(1) Satellite institutions

University of Texas Southwestern Medical Center (UTSW)

The three Satellite PIs (Joseph Takahashi, Robert Greene, and Carla Green) have conducted research collaboration under the collaborative research agreements and/or the sponsored research agreements since FY 2013. C. Green engages in the sponsored research of RNA-Seq analysis of sleep-deprived mice, and R. Greene covers the sponsored research on sleep homeostasis and the sleep-awakening regulation of adenosine. J. Takahashi conducts the sponsored research on circadian rhythm control of sleep.

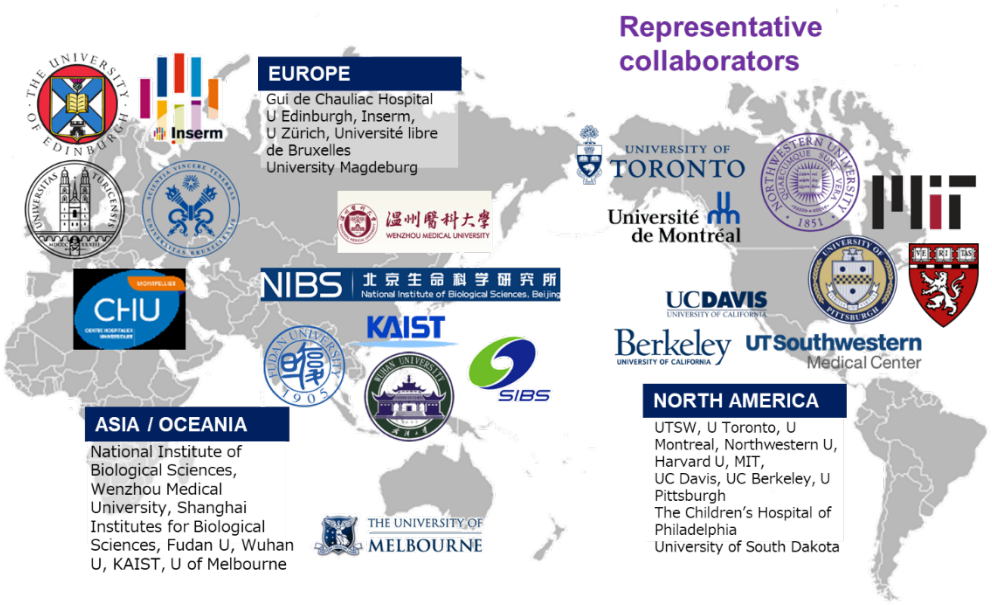
National Institute of Biological Sciences (NIBS)

As of January 2019, Q. Liu was appointed to the Investigator of NIBS, Beijing and a new collaborative research agreement was executed for the cross-appointment between NIBS and University of Tsukuba. He serves as Investigator at NIBS and professor at IIIS with relative efforts of 92:8, respectively. His primary research commitment is to his lab at NIBS, which serves as the first overseas satellite of IIIS in Asia.

(2) Partner institutions

From FY 2018, we started a collaboration with Sleep Disorder Centre, Neurology Department, Gui de Chauliac Hospital, Montpellier, France for the purpose to discover human genetic factors of sleep disorders using their biobank of sleep disorder patients. IIIS performs exome and whole genome sequences of DNA samples extracted from their clinical samples of sleep disorder patients such as narcolepsy and idiopathic hypersomnia in Sleep Disorder Centre. In FY 2019, we got very promising data by the exome analysis as described in 1-1.

We also perform many collaborative researches under material transfer agreements on animal models or compounds, and published many collaborative papers as the following schematic figure shows.



3-2. Center's record of attracting and retaining top-world researchers from abroad

The overseas PIs, R. Greene and Q. Liu have actively participated in the research activities at IIIS. Greene contributed to IIIS through his research activities in University of Texas Southwestern Medical Center (UTSW) as Satellite PI, as well as his function as Co-PI in Greene/Vogt Lab in IIIS. He stayed at IIIS for 58 days during 6 visits to Japan in FY 2019. On the other hand, Liu as Co-PI in Liu/K. Sakurai Lab stayed at IIIS for 26 days on 5 visits to Japan in FY 2019. Both Greene and Liu actively contribute to the management of IIIS by participating in the PI meetings held monthly, even when absent from the institute, via Skype or Zoom from UTSW or NIBS. They also actively participate in important events including the symposia hosted by IIIS and the annual site visits.

To 8th WPI-IIIS Symposium co-hosted with Ph.D. Program in Humanics and the 36th Takamine Conference was held on November 26, 2019 at Tokyo Conference Center, and outstanding foreign researchers were invited from abroad in order to introduce the latest achievements in sleep research and relevant fields. On the following day, we invited one of the foreign guests to IIIS to hold the post-symposium seminar to let researchers in the Tsukuba community share the recent progresses in sleep research.

We hosted 19 WPI-IIIS Seminars in FY 2019, where we invited domestic and foreign researchers in sleep/neuroscience and relevant fields almost every other week; 9 speakers from overseas gave lectures and the ratio of foreign researchers was 47% of the total seminar speakers in FY 2019. Consequently, 166 seminars have been conducted since the inauguration in December 2012.

Another thing especially worth mentioning is that the number of foreign researchers visiting IIIS has increased significantly. As shown in Appendix 5, 17 researchers attracting a lot of attention visited IIIS besides PIs and the speakers of IIIS Symposiums and IIIS Seminars. They all got an introduction to IIIS and its studies by the Center Director, found some potential for collaboration and enjoyed the visit very much. The increase of visitors from abroad is an indication suggesting that IIIS has become a globally attractive and well-known institution.

3-3. Center's record of holding international symposia, workshops, research meetings, training meetings and others

IIIS organizes international symposia annually since the establishment in FY 2012. In FY 2019, we co-hosted WPI-IIIS Symposium with Ph.D. Program in Humanics, which was launched in FY 2018 as one of the Doctoral Programs for World-leading Innovative & Smart Education (WISE Programs) of MEXT, and 36th Takamine Conference, which commemorates Yanagisawa's 17th Takamine Memorial Daiichi Sankyo Prize. Under the theme of "Fusion of Biomedical and Physical/Informational Sciences in Neurobiology," we invited prominent neuroscientists from Japan and abroad who actively

pursue interdisciplinary research, and enjoyed lectures and scientific discussions including unpublished data. The joint symposium attracted more than 200 participants from academia as well as industries, beyond the boundaries of the research fields, and largely contributed to inspire new ideas and expanded collaboration opportunities. In addition, on the following day in Tsukuba we held the post-symposium seminar with Dr. Henrik Bringmann from Philipps University of Marburg, one of the speakers at the joint symposium. The seminar was also a great opportunity for all participants to intensively discuss about his sleep research using nematode.

With regard to the next IIIS Symposium, we are planning to hold it jointly with "the 45th Annual Meeting of Japanese Society of Sleep Research (JSSR)" and a project of JST's Core Research for Evolutional Science and Technology program (CREST), "OPTBIO." Since we successfully got funded ¥4,000,000 by CREST as a subsidy for the promotion of globalization, we are preparing an attractive program inviting more of distinguished and eminent researchers. It would be our responsibility as a leading institute for sleep science to contribute to the development and progress of sleep research by holding the international and exciting symposium.

3-4. Employment of young researchers at the Center and their job placement after leaving the Center

IIIS actively has engaged in open recruitment by placing job advertisements on web-sites such as the homepages of IIIS and University of Tsukuba, jREC-IN jobsite and Nature Jobs, etc. After the renewal of IIIS's website, it became possible for foreign researchers to select and apply directly for the laboratory matching to their interests and expertise. The number of applications for researchers has been gradually increasing.

On the other hand, in addition to posting job advertisements, we have employed some brilliant researchers through the continued efforts in international recruitment through networks of PIs. We have regularly invited speakers from abroad for the IIIS Seminar series and made use of these opportunities to look for early-career PIs and postdoctoral researchers. In FY 2019, three foreign researchers (2 Chinese and 1 American) joined us.

Ex-IIIS young researchers and faculties acquired positions in top-level universities; Yu Hayashi (a junior PI) was promoted to a full professor in Human Health Science, Kyoto University, Zhiqiang Wang (a postdoc) was appointed to a senior research fellow (PI) at Harbin Institute of Technology, and other researchers, Takato Honda, Chia-Ying Lee, Yan Zhang and Jing Ma obtained postdoc positions in Massachusetts Institute of Technology, Fred Hutchinson Cancer Research Center, Shenzhen University College of Materials, and Harbin Institute of Technology, respectively. Sayaka Ohrui (a Ph.D. student) acquired a position of an assistant professor at Meiji Pharmaceutical University after spending one year as a researcher at Research Foundation Itsuu Laboratory and Mustafa Korkutata (a Ph.D. student) acquired a position of a postdoctoral fellow in Harvard Medical School. Research achievements and experiences at IIIS contribute to the career development, and the number of the young researchers acquiring positions outside IIIS has been increasing.

3-5. System for supporting the research activities of overseas researchers and students

University of Tsukuba has a department, "Global Commons, International Exchange Support Office" which engages in livelihood support for foreign researchers and their families. They provide information on accommodation for foreigners in and outside the university and daily life in Tsukuba, and offer services including Japanese classes, proxy application for the certificate of eligibility (visa), some aid for various procedures and paperwork preparations, etc. Foreign IIIS researchers benefit significantly from the Support Office.

Japan International Science and Technology Exchange Center (JISTEC) operate the Tsukuba Office and IIIS has concluded the agreement on support for foreign researchers by JISTEC staffs. They offer the paid services at minimal costs of attending to foreign researchers for the residence registration at City Hall, opening a bank account, etc. Further, many IIIS foreign researchers use their accommodation (Ninomiya House and Takezono House) managed by Projects to Support Living and Housing for Foreign Researchers/Management Services for International Accommodation of JISTEC.

Some researchers use the accommodation for foreign researchers/faculties on the campus of the university, at a highly convenient location and with well-organized support. Newly built Global Village, an international house and a short-stay dormitory, accepts students and short-term trainees from overseas and the on-campus Shopping Plaza, composed of a supermarket (KASUMI) and a cafe (Saza Coffee) have improved the welfare and convenience of students, faculties and staffs especially

of ones from overseas.

Conversely, in IIIS, we translate various forms into English, including documents of various regulatory applications and formats/documents related to employment, personnel affairs and general affairs. Other documents are also converted into English as necessary. We also support our foreign researchers by making sure all notices and announcements received from the university administration are translated into English from the original Japanese by the IIIS Administration. In this way, our researchers are able to stay aware of university-wide as well as institutional information.

The Research Strategy Team in the IIIS Administration is in charge of a wide range of responsibility relating to budget planning, personnel planning, competitive funding application, conclusion of contracts, patent application, etc. All the members of the team are fluent in English and are able to support foreign PIs equally.

We have equally assigned secretaries proficient in English with full of hospitality to all labs to provide foreign PIs, researchers and students with sufficient supports.

We created a new support system for a newly arrived foreign researcher, "Buddy System," assigning a personal mentor, "Buddy" for him/her in FY 2019. The system has been functioning efficiently.

We have accepted 31 international students/trainees in FY 2019 through various systems to accept foreign students to University of Tsukuba, as shown in the following table. We accepted 6 students from China, Mexico, USA, Ireland, France and Taiwan through the Tsukuba Short-term Study Program (TSSP), which allows even short-term trainees to use the student dormitory at a nominal fee and yet requires no entrance and tuition fees. The bylaw for TSSP was revised in March 2016, according to our request to extend the longest period of stay from 3 months 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 1 student 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 and capabilities between University of Tsukuba and University of Bordeaux.

IIIS accepted 5 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.

We also accepted 2 undergraduate students through JST Sakura Science Exchange Program which invites people from Asian countries and others to Japan through Sakura Science Plan in the collaboration of industry-academia-government, to introduce and offer experience in Japanese science and technology.

Other than above, IIIS took care 2 undergraduate and 15 graduate foreign students through Ph.D. programs in University of Tsukuba.

Concerning financial support for foreign students, 2 graduate students, were approved for Research Assistants to obtain monthly wages in FY 2019. For undergraduate student, we approved "IIIS Scholarship" which supports a student who would like to go on to a graduate school in University of Tsukuba to continue a dissertation study in IIIS and does not get a financial support such as TA. This supporting system was newly established in July 1, 2019, originally by IIIS.

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

Name	Status	Country	Instructor	Duration in FY 2019	Remarks
Can Liu	Graduate	China	Liu	Apr 1, 2019～Jun 30, 2019	TSSP
Manuel Saldaña Aguado	Graduate	Mexico	Sakurai	Apr 1, 2019～Jul 19, 2019	TSSP
Midori Kisanuki	Undergraduate	USA	Abe	May 13, 2019～Jun 28, 2019	TSSP
Sarah Halpin	Graduate	Ireland	Tokuyama	Jul 8, 2019～Sep 30, 2019	TSSP
Paulina Lubeigt	Undergraduate	France	Yanagisawa	Jul 16, 2019～Jul 26, 2019	TSSP
Feng Liang	Undergraduate	Taiwan	Yanagisawa	Jul 16, 2019～Jul 26, 2019	TSSP

Ana Dorison	Graduate	France	Lazarus	Jan 14, 2020～Mar 31, 2020	CiC
Chandra Louis	Graduate	Indonesia	Sakurai	Apr 1, 2019～Sep 30, 2019	MEXT
Zhang Zhongwen	Undergraduate	China	Sakurai	Oct 1, 2019～Mar 31, 2020	MEXT
Kseniia Prokofeva	Graduate	Russia	Hirano	Oct 1, 2019～Mar 31, 2020	MEXT
Vergara Garcia	Graduate	Chile	Sakaguchi	Oct 1, 2019～Mar 31, 2020	MEXT
Xuhao Zhou	Graduate	China	Lazarus	Apr 1, 2019～Aug 31, 2019	MEXT
Veila	Undergraduate	Indonesia	Yanagisawa	Feb 16, 2020～Feb 22, 2020	JST
Le Nguyen Lam Ngoc	Undergraduate	Vietnam	Yanagisawa	Feb 16, 2020～Feb 22, 2020	JST
Pei His Wu	Undergraduate	Taiwan	Sakaguchi	Oct 1, 2019～Mar 31, 2020	U.Tsukuba
Yuteng Wang	Graduate	China	Sakaguchi	Apr 1, 2019～Mar 31, 2020	U.Tsukuba
Jiahui Yu	Graduate	China	Sakaguchi	Jul 1, 2019～Mar 31, 2020	U.Tsukuba
Juan Carlos Almanza	Graduate	Colombia	Yanagisawa	Apr 1, 2019～Mar 31, 2020	U.Tsukuba
Mahmoud Asmaa	Graduate	Edypt	Yanagisawa	Oct 1, 2019～Mar 31, 2020	U.Tsukuba
Choi Jinhwan	Graduate	Korea	Yanagisawa	Apr 1, 2019～Mar 31, 2020	U.Tsukuba
Park Minjeong	Graduate	Korea	Yanagisawa	Apr 1, 2019～Mar 31, 2020	U.Tsukuba
Kittipob Suphachalasai	Graduate	Thailand	Toda	Oct 1, 2019～Mar 31, 2020	U.Tsukuba
Han GoEun	Graduate	China	Vogt	Apr 1, 2019～Mar 31, 2020	U.Tsukuba
Like Jiang	Graduate	China	Abe	Apr 1, 2019～Mar 31, 2020	U.Tsukuba
Lee Chia Ying	Graduate	Taiwan	Liu	Apr 1, 2019～Aug 31, 2020	U.Tsukuba
Asher Gregor	Graduate	USA	Liu	Apr 1, 2019～Nov 30, 2020	U.Tsukuba
Liu Chin Yao	Graduate	Taiwan	Hayashi	Apr 1, 2019～Mar 31, 2020	U.Tsukuba
Tsai Chia-Jung	Graduate	Taiwan	Hayashi	Apr 1, 2019～Mar 31, 2020	U.Tsukuba
Chen Chung Kuan	Graduate	China	Hayashi	Apr 1, 2019～Mar 31, 2020	RA
Lou Tingting	Graduate	China	Liu	Apr 1, 2019～Mar 31, 2020	RA
Ruth Li	Undergraduate	China	Sakurai	Apr 1,2019～Mar 31, 2020	IIIS Scholarship

3-6. Others

Efforts for fostering young researchers.

(1) International Sleep Research Training Program

We have recently been appointed as a training site of the International Sleep Research Training Program (ISRTP). ISRTP was formalized by Word Sleep Society (WSS) in 2019 in order to prepare sleep trainees from various countries throughout the world for future leadership in basic and/or clinical sleep research.

The aim of the ISRTP program is to provide such trainees with an opportunity of training at major academic institutions such as WPI-IIIS. The trainees can acquire sleep research skills and observe management of patients with sleep disorders from experienced scientists and clinicians. This program seeks to enrich the growing field of sleep medicine and research with future sleep research leaders.

The trainees will be matched to sleep research mentors, WPI-IIIS PIs, based on their research plans. Each trainee must have funds to support his or her trainee year at the host institution. The program will provide trainees with travel funds to participate in two major international sleep meetings.

Through this program, we are seeking best trainees/mentees from all over the world to be trained and let them vigorously communicate and maximize their potentials at our world's premier institute.

(2) International Grants

IIIS encourages young researchers to get international experiences. Two researchers have gotten the travel grants for the international meetings in FY 2020; the Society for Neuroscience Annual Meeting, International Brain Research Organization in Washington D.C., USA, 24-28 October, 2020, and the 12th FENS Forum of Neuroscience, the Japan Neuroscience Society and Federation of European Neuroscience Societies in Glasgow, UK, 11-15 July, 2020.

4. Making Organizational Reforms

* Describe the system reforms made to the center's research operation and administrative organization, along with their background and results.
* 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.
* Describe the center's operation and the host institution's commitment to the system reforms.

4-1. System reforms advanced by WPI program and their ripple effects

We have made significant efforts to improve administration systems, rules and bylaws of University of Tsukuba to realize objectives/policies of IIIS and the WPI program as follows. We will continue the efforts of the system reforms in cooperation with the university.

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 the university by learning from the merits and virtues in the organization of "departments" in major U.S. universities. 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, Yanagisawa, who had served as a professor/PI for 24 years at University of Texas Southwestern Medical Center (UTSW). Other characteristics of this "department-style" organizational operation we would like to adopt include:

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

Indeed, all of these characteristics are perfectly realized in the organization and operation of IIIS. In FY 2019 we added 1 PI of an assistant professor, H. Toda, and there are nine early-career PIs in the core group of IIIS. The labs and offices in IIIS Building are designed as physically and psychologically open structures, which enable the flexible 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.

Decision-making system in the center

For important matters concerning the operation of IIIS, all decision-making was done in accordance to the Center Director's top-down approach. So that the intention of the Center Director takes effect quickly, organizational bylaws and other related regulations continue to be revised or enacted. By positioning IIIS as an independent research center in University of Tsukuba, wide-ranging autonomous operations, including personnel affairs, environmental improvement and budget planning are secured.

Introduction of a system to evaluate research results and ability-linked salary system

In FY 2017, IIIS introduced a simple system to evaluate achievements of faculties and researchers. In the new system, they are requested to update their own CV and provide it to their appraisers, PI and the Center Director. Further, they are asked to perform self-evaluation by using a simple form for the achievement evaluation. After the self-evaluation, PI and then the Center Director are supposed to make assessment of their achievements. The achievements include published papers and books, granted external funding, research alliance with public and for-profit organizations, outreach activities, and contribution to IIIS activities. We consider the salary-raise based on this appraisal to build a system of merit-based compensation. The salaries for the administrative staffs are determined by the Center Director, based on the opinion of the Administrative Director.

Authority over personnel matters and simplification of the appointment system

IIIS Personnel Committee was established in FY2012 and distinctive authority over personnel matters was assigned. Only 3 research centers in the university, i.e., IIIS, TARA Center and CCS, are given such authority over personnel matters. In particular, the appointment system of IIIS is simplified to be comprised with two steps, namely the intensive deliberation at IIIS Personnel Committee and the approval at Headquarters Personnel Council of the university, allowing speedy judgment and appointment by the leadership of the Center Director.

4-2. Arrangement of administrative support staff and effectiveness of support system

IIIS Administration provides support services so that researchers could entirely focus on research, under the leadership of the Administrative Director. Having served as Senior Director of the research institute of a pharmaceutical company, the Administrative Director has expertise of research management and strategies. He is assisted by the Vice Administrative Director and the following four teams: the General Affairs (3 persons), the Accounting (3 persons), the Research Planning (3 persons) and the Outreach & Communication (2 persons).

The Vice Administrative Director, who has served many years as a section chief at University of Tsukuba headquarters, concurrently serves as the leader of the General Affairs and the Accounting. The Vice Administrative Director, making use of his networks, strives to resolve various issues that require coordination with the university headquarters.

The Research Planning & Management Team is led by a Ph.D. (Associate Professor) who has real comprehension of research details and a good knowledge of contract and patent matters. He has taken charge of preparing collaboration agreements and patent applications expeditiously in collaboration with law firms and patent firms. As in the previous fiscal years, the team received a URA who was assigned from the university headquarters to provide services of pre-awards and post-awards grant management.

The Outreach & Communication Team is led by a science communicator who has a good knowledge of outreach activities. She exercises active leadership in a range of activities, including hosting the international symposiums and IIIS seminars, preparing press releases and handling the media, and providing information timely.

With all the teams working together, IIIS Administration itself has taken a leadership role in the promotion of research projects across several labs at IIIS, the acquisition of funding for large-scale research projects such as the Exploratory Stage of JST-MIRAI Project, and other events, which resulted in highly acclaimed outcomes.

Another point to note is that the use of English is strongly encouraged as the official language of IIIS, with approximately 70% of the administrative staff being bilingual and able to communicate smoothly with foreign researchers. Within IIIS, documents and papers are prepared in English or in 2 languages, Japanese and English, in principle.

4-3. Record of host institution support and its effects

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

1. The university established the Organization for the Support and Development of Strategic Initiatives, and IIIS receives ¥10 M for management expenses as the support from the Organization every year.
2. The Department of Research Promotion, as a counterpart in the university headquarters to IIIS, supports various office procedures including the applications for competitive funding.

3. The university supports most of the personnel cost of Vice Center Director, T. 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. A URA has been also assigned to the Research Planning and Management Team.
5. IIIS rents for ¥70 M/year a part of the IIIS Building (2,000 m^2) that was expanded by the university funds, while the University bore more than ¥88 M of utility costs of IIIS Building.
6. From April 2019, the university let IIIS use the research spaces (211 m^2) in Innovation Medical Research Institute at minimal cost to build up the Human Sleep Lab., as described in 6-2.

4-4. Others

Internal grant system

An internal grant system has been introduced as rescue funding. This system is mainly intended for researchers who failed to acquire competitive research funding such as Grants-in-Aid for Scientific Research, and such researchers are invited to apply for it in April. In order to ensure the neutrality of the review process, three members holding Ph.D. in the Administration serve as reviewers and perform a face-to-face interview with every applicant to examine the proposals and prioritize them.

IIIS Research Assistantship System

We have continued the IIIS Research Assistantship (RA) system to encourage students to go on to Ph.D. courses since FY2017. Graduate students in the doctoral program (or after 3rd year of 5 year graduate program) can apply for the IIIS RA only if he/she applied for the JSPS Research Fellowship for Young Scientists (DC1/DC2) but unsuccessful. Graduate students in the master's program/1st or 2nd year of 5 year graduate program can apply for the IIIS RA only if he/she is committed to go to the Ph.D. program. Selection of applications have been conducted by the Center Director and the Admin staff members.

IIIS Scholarship

In FY 2019, to promote research in IIIS through providing motivated young students with financial supports, we introduced a new scholarship program, IIIS Scholarship for undergraduate students that would like to go on to a graduate school in University of Tsukuba to continue a dissertation study in IIIS but get no financial supports currently. The IIIS Scholarships awardees shall be students of 5^{th} or 6^{th} grade of School of Medicine in the university that are committed to go directly to the Ph.D. program in Biomedical Sciences/Clinical Sciences, Graduate School of Comprehensive Human Sciences, or trainees of the Tsukuba Short-term Study Program who are deemed by the Center Director that they are excellent and in need of financial support. This scholarship has been covered by the funds based on contributions and donations to IIIS.

Mental Care Programs in IIIS

We support students not only financially but also mentally. The mental care counseling for students has been conducted once a year since FY 2017. When a student in trouble is found, we offer additional counseling by the Admin staff including the Administrative Director to shoot the trouble.

Online Residence Application Procedures

IIIS accepts many foreign researchers, and we recently introduced the online residency card application procedure for the first time in University of Tsukuba. The international office in the university headquarters is quite conservative, and they have no plan to apply for this online system. Since we heard that it was possible for a department or a center of the university to use this system using the corporate ID of the university, we applied for the registration as the user at Mito Branch Office, Tokyo Regional Immigration Bureau. The online system will eliminate the need for IIIS foreign researchers (and possibly foreign students) to go to the Immigration Office in Tokyo and let them save a lot of time. This is just one example of our "system reforms," to be spread over the entire university in future.

5. Efforts to Secure the Center's Future Development over the Mid- to Long-term

* 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 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. Future prospects with regard to the research plan, research organization and PI composition

As discussed in "1-1. Background and objectives of sleep research in IIIS," we have added to our major objectives the fourth one, i.e., "to elucidate the fundamental mechanisms of hibernation regulation." Our recent finding of a group of neurons in hypothalamus (Q neurons) that induce hibernation in mice let us expand the scope of our research from sleep to hypomobile behaviors. Many behaviors of animal, e.g., feeding, reproduction and aggressive behavior, are consisted of motions, while two hypomobile behaviors, sleep and hibernation are regulated hypomobile states essential for life support.

The expansion of the research scope requires expansion of research organization as well. The current organization of IIIS was planned to perform only the sleep research, and we shall enlarge the research capacity to spare appropriate research resources for hibernation studies. Implementation plans of the hibernation studies are comprised of enlarging Sakurai/Hirano Lab and recruiting additional satellite PIs in and out of University of Tsukuba. Candidates of the satellite PIs include M. Matsumoto, Faculty of Medicine, University of Tsukuba for non-human primate study, and G. Sunagawa, Laboratory of Retinal Regeneration, RIKEN Kobe for the study of peripheral organ regulation in hibernation, and H. Ando, Center for Artificial Intelligence Research, University of Tsukuba for analysis of central nervous system-peripheral organ network in hibernation.

The research organization for the sleep research in IIIS shall be also expanded to some extent to accommodate studies of system biology and AI. According to the advice made by the Working Group at the Site Visit, we intend to undertake studies of system biology to analyze interactions between central nervous system and peripheral organs during sleep as well as hibernation. We also plan to analyze big data of sleep and epidemiology in collaboration with S'UIMIN Inc., which will launch a service of sleep diagnosis for the night of consecutive 7 days at home. Collecting epidemiological data from customers for the home sleep diagnosis voluntarily, the big data will be constructed and subjected to AI analysis to reveal correlation between sleep deprivation and chronic disease. In IIIS we will establish System Biology/AI Core, a virtual unit of computer science, inviting, H. Ando, Policy and Planning Sciences, University of Tsukuba, H. Kitagawa, Center for Computational Science, University of Tsukuba, and H. Ozaki, Faculty of Medicine, University of Tsukuba, as Collaborative PIs.

The rest of the research organization for the sleep research shall be maintained as it is even after the program funding ends. The core group of IIIS responsible for sleep research is comprised of neuroscience/molecular genetics, pharmaceutical science and experimental medicine/human physiology. The core group continues pursuing three objectives of sleep research to achieve elucidation of the total pictures of sleep/wake regulation and functions of sleep by 2030. Composition of PIs in the core group shall be also maintained in principle, except for mandatory retirement and its substitution.

5-2. Prospects for securing resources

Since the five-year extension of the WPI program was not granted to IIIS, we seek alternative financial resources that substitute for the WPI subsidy as the basal funding, in combination of several funding programs, grants, donations and incomes, rather than a single source of financial support.

The biggest efforts are being made to acquire large competitive research funding offered by governmental financing agencies such as Japan Science and Technology Agency (JST), Japan Society for the Promotion of Science (JSPS), Japan Agency for Medical Research and Development (AMED) and New Energy and Industrial Technology Development Organization (NEDO). The current targets are "Moonshot Research and Development Initiative" for which JST (Cabinet Office) has been inviting application since February 20, 2020, and the full-scale project of "JST-Mirai (Future Society Creation) Program." Our research plan has been already adopted for the exploratory project of JST-Mirai program since FY2019 and we aim to promote it to the full-scale project

starting as of April 1, 2022. A scale of the expected budget of the Moonshot R&D and the JST-Mirai (full-scale) programs in combination is comparable to the WPI subsidy.

Among potential applications of synthetic hibernation, NASA's plan of interplanetary space flight to Mars may give rise to an urgent need for development of the technology applicable to astronauts. We may thus propose the collaboration to NASA and/or DARPA to obtain a large financial supports for the study in IIIS.

We also seek supports (donations) from foundations promoting scientific research, e.g., the Kavli Foundation promoting neuroscience studies in conjunction with its Brain Research program, and/or TOYOTA Mobility Foundation supporting projects to innovate the mobility.

In the longer term than a decade, we try to establish an ecosystem with S'UIMIN Inc., which is a spin-out venture from IIIS. IIIS provides S'UIMIN with IP rights of business seeds created from achievements of IIIS, and S'UIMIN develops and implements them into its business (or license them to global companies after demonstrating a proof-of-concept) to gain profits. A significant part of profits shall be returned to IIIS as the reinvestment to create next business seeds, resulting in an ecosystem between IIIS and S'UIMIN. The ecosystem would secure IIIS stable incomes and operation in the long-term.

5-3. Measures to sustain the center as a world premier international research center after program funding ends

IIIS receives ¥560 million/year of WPI subsidy, which account for XX% of the total annual budget of IIIS. As we succeed in obtaining more competitive research funding, weight of the WPI subsidy has become smaller. Personnel expenses of the core group of IIIS amounting to more than ¥XXX million/year, however, are still covered mostly by the WPI subsidy. Another large expenses covered by the WPI subsidy is ¥XX million/year of the rent for a part of the IIIS Build. To make IIIS sustainable, we have to secure financial resources more than ¥XXX million/year that substitute for the WPI subsidy as the basal funding. As discussed above, we strive to secure sufficient basal funding in combination of several sources of financial support.

It is the unique and salient feature of IIIS that it has been built up as a *de novo* WPI center. Among 20 PIs in the core group of IIIS, PIs recruited from the outside of University of Tsukuba occupy 90%, while ratios of PIs recruited externally in ITbM and ELSI are only 54% and 58%, respectively (WPI Progress Reports 2018). There were only 10 PIs in the core group in FY2013, and it took us 6 years to double the number by recruiting the best PIs qualified for our requirements from around the world. Thus most of PIs, except for the Center Director and the Vice Center Director and a few tenure-track PIs, have been appointed as a contract employee with a limited-term. Because of Labor Contract Reform Act, the renewal of their contracts is limited up to 10 years. In order to keep qualified PIs and make IIIS sustainable as a world premier international research center, we have to grant tenure to them before 10 years of the term completes. The President of University of Tsukuba has repeatedly stated at the WPI Program Committee Meeting that PIs with a proven track record of achievement should receive the status of tenure. A candidate for tenure shall be nominated by the Center Director with consent of the Vice President responsible for human affairs and subjected to the tenure review by the IIIS Personnel Committee to determine whether the candidate should be recommended to the President for tenure.

5-4. Host institution's organizational reforms

IIIS has given a major impact on the reform of University of Tsukuba. During the third mid-term plan starting from FY 2016, the university aims to pursue the 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 has made a plan of reorganization/restructuring/merger of all research centers and is implementing it during the period of the 3rd mid-term plan. Based on the plan the research centers have been classified by function into the Advanced Research Centers and the Research Support Centers. The former has been further classified as R1 (World-class Research Center), R2 (National-class Research Center), R3 (Developing Research Center), and R4 (Research Unit) to facilitate strategic resource allocation. Center for Computational Science (CCS) and Life Science Center for Survival Dynamics, Tsukuba Advanced Research Alliance (TARA) are classified as the R1 status of World-class Research Center

in physics and bioscience, respectively, but the status of all research centers shall be reviewed every five years.

In addition to the research center's reorganization and classification, the university decided to establish Organization for Development of Global Research Centers in order to aid the development of the global research centers through the comprehensive support provided by the creation of an 'On-campus Special Zone for Research Strategy' (provisional name) and strategic allocation of the university's research resources.

IIIS and R1-accredited CCS and TARA, are the first members of the Organization, which aims to expand horizontally among these centers the tasks/achievements of promoting the advanced and interdisciplinary researches, internationalization, and reforming systems thus far headed by the IIIS. Specifically, with Vice President responsible for research as the Organization's Director, an office of strategic planning is to be established, along with an academic coordinator for strategic collaboration and a support division.

As of March 26, 2020, University of Tsukuba officially established Organization for Development of Global Research Centers comprised of CCS, TARA, and IIIS. Much is expected of IIIS to contribute for the success of the Organization by the active sharing of experience, knowledge, and know-how accumulated at IIIS.

6. Others

* Describe what was accomplished in the center's outreach activities last year and how the activities have contributed to enhancing the center's "globally visibility." In Appendix 6, describe concretely the contents of these outreach activities. In Appendix 7, describe media reports or coverage, if any, of the activities.
* In addition to the above 1-5 viewpoints, if there is anything else that deserves mention regarding the center project's progress, note it.

6-1. Characteristic outreach activities

(1) Outreach events aimed at face-to-face communication

In order to enhance the visibility of IIIS, we opened a booth to promote our research achievements and the importance of sufficient sleep in several science events for general public such as "The Super Science High School Annual Research Meeting," "WPI Science Symposium," and "Kagaku-Zammai in Aichi 2019."

For example, in "Kagaku-Zammai," which was a science event for high school students and teachers in Aichi prefecture, we had so many times of requests to give talk shows about sleep science, where the audience selected some topics of their own interest from among six. Our talk, which included not only sleep physiology and research achievements of IIIS, but also the trivia of sleep, attracted more than 300 audiences in total. A similar booth was also opened at "WPI Science Symposium," which was mainly for adults, and was really well received.

These events provided us with opportunities for open dialogue with general people, and greatly contributed to our mission to disseminate information on sleep and health to the society.

(2) Development of new approach for outreach: Nico Nico Cho-Kaigi

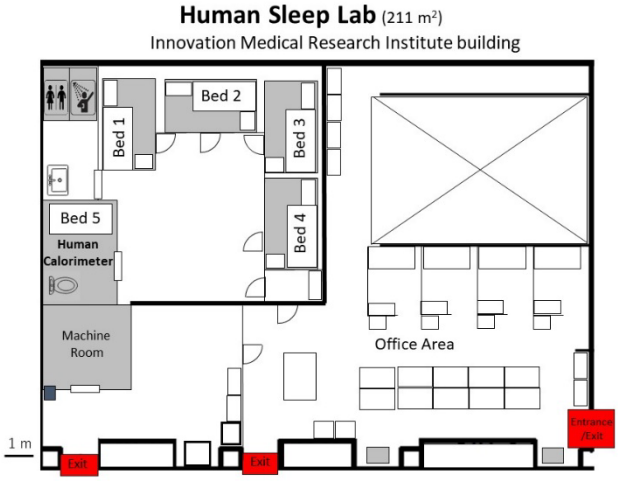
Since FY 2017, we have been working on new interactive outreach activities via internet broadcasting collaboratively with Nico Nico (DWANGO Co., Ltd.). In FY 2019, we joined Nico Nico Cho-Kaigi (Super Meeting), an on-site event, which was held at Makuhari Messe on April 27 and 28. In order to introduce the cutting-edge sleep science, we had a panel exhibit at Cho-Suimin (Super Sleep) Booth and broadcasted two Nico Nico Live programs with Yanagisawa and T. Sakurai. In the two day event, about 1,000 people visited the booth and 40,000 people watched the live broadcasts. They all asked out of their curiosity about sleep and enjoyed talking with Yanagisawa and Sakurai. This event was a great opportunity for the effective outreach, taking advantage of both onsite and online.

(3) Education programs for junior/senior high school and college students

In order to raise interest in sleep science and develop the next generation of scientists, we have accepted visitors from junior/senior high schools and provided various kinds of educational programs such as lectures, demonstration of experiments, round-table talks with researchers, lab tours, and so on.

In FY 2019, we accepted 20 of school visits (two were canceled due to the concern of COVID-19), which was the largest number since the establishment of IIIS. Our educational programs are highly

evaluated, and at present 7 schools visit IIIS on a regular basis. Importantly, "Sleep Science Challenge" with Kumamoto prefectural Uto Senior High School, which has annually held since FY 2013, has resulted in the recruitment of students engaging sleep research at IIIS, while in the high school the students began voluntary efforts to improve their sleep habits. Hibiki Okamura, who had visited IIIS in 2014 and 2015 as a student at Uto Senior High School, entered University of Tsukuba in 2019 aiming to join sleep research at IIIS and began her undergraduate dissertation study at Toda lab. In addition, 5 schools from abroad visited IIIS in FY 2019 and the number of foreign visitors has been increasing year by year.



(4) Media Coverages

Since the number of media coverage in FY 2018 reached 180, the highest number so far, it appeared that our reputation as one of the world's leading research institute for sleep was well established, and we changed our media strategy toward the next stage. Due to careful screening of collaborating media, the number of media coverage in FY 2019 was 87, which was significantly lower than the previous year. However, it should be noted that several media featured IIIS at unprecedented scale. For example, the featured articles on "Newton" and "Newton Extra Issue," which were both supervised by Yanagisawa, devoted a full of 50 pages to the introduction of cutting-edge sleep science including achievements of IIIS. It received great responses from a wide range of people who are interested in sleep science.

Various overseas media including "Gehirn & Geist" (a popular science magazine in Germany), "The Early Edition with Stephen Quinn" (a radio program in Canada), and "Nature Asia" also contributed to a great increase of international recognition of IIIS.

(5) Events for IIIS members and the university staff

As an internal event to encourage open communication, we have already had the Brie & Bordeaux (B&B) more than 20 times so far. In addition to this, we planned "IIIS Retreat," which is an excursion for all IIIS members to enjoy lectures by PIs, scientific discussion, and some sightseeing. The executive committee was organized by students from several labs, and it organized the whole event with the support by the Admin, but unfortunately we had to postpone it to the next year at the last minute due to the concern of COVID-19.

Moreover, in order to promote better understanding of IIIS and its activities, we held "IIIS Open House" for administrative staffs in the headquarters of University of Tsukuba. This event has led to enhanced cooperation with various departments in the university and effective PR activities of IIIS. We also believe that we can contribute to the system reform throughout the university by sharing our management and operation know-how.

6-2. Human Sleep Lab

New research facility for human sleep physiology, Human Sleep Lab (HSL) was newly established in University of Tsukuba, Innovation Medical Research Institute building (COI Building) in April 2019.

In HSL there is 4-bed sleep laboratory in which temperature, humidity and illuminance can be controlled, and polysomnography (PSG) can be performed in 4 measuring chambers simultaneously. The bed in each chamber is equipped with reclining function enabling a wide variety of experimental protocols. In addition, the facility for energy metabolism measurement, "Human Calorimeter," with the world's highest level of time resolution has been relocated to HSL from IIIS Building. HSL is one of the leading facilities for human sleep research in Japan.

We held the opening ceremony of HSL on April 15, 2019. In WPI-IIIS Seminar held as a part of the ceremony, we invited Dr. Kingman Strohl from Case Western Reserve University, Dr. Marry Morrell from Imperial College London, and Dr. Shigenobu Shibata from Waseda University as speakers, and had lively discussions on the latest developments in sleep research. After the seminar, a lab tour of

HSL was conducted by Satoh, Tokuyama, Kanbayashi and Abe, followed by a reception. Having more than 100 participants, the opening ceremony was concluded with great success.

6-3. Ph.D. Program in Humanics

In FY 2018, under the leadership of the Center Director and in close cooperation with key members of the Faculty of Medicine in University of Tsukuba, including the Dean and Associate Dean of the Faculty, we applied for the Doctoral Program for World-leading Innovative & Smart Education (WISE Program) of MEXT, and presented a proposal to create the Ph.D. Program in Humanics. Fortunately, our application was adopted in October 2018. The Ph.D. Program in Humanics aims to create a new academic discipline called "Humanics," which merges high levels of expertise in a) biomedical sciences and in b) physical sciences/engineering/informatics.

The Ph.D. Program in Humanics aims to train a new generation of leaders who have knowledge and skills at the doctoral level and sufficient scientific expertise to merge two disciplines, and who have the ability to apply the expertise to make contributions to society. For this purpose, the program features bi-disciplinary education system in which each student receives guidance from two mentors - one in biomedical sciences and another in physical sciences/engineering/informatics.

One well-known successful example of Humanics is the HAL robot suit by CYBERDYNE Inc., a startup company originating from University of Tsukuba, which was developed by combining neuroscience and robotics engineering. The program envisions cross-disciplinary research, such as analysis of big data on sleep through the combination of sleep medicine and artificial intelligence technology, and this is expected to offer greater opportunities for interdisciplinary studies at IIIS and other fields. Moreover, we aim to attract excellent students through this program. For students who have already conducted research in sleep science, the program will provide more options to widen their study subjects, raising expectations that it will facilitate the training of young researchers.

Four out of the 14 students enrolled in FY 2020 have selected PIs in IIIS as one of their dual-mentors, and a total of seven students conduct their dissertation studies in IIIS, including the three students enrolled last year. Many of these students have backgrounds in sleep research, but a student with the background of informatics enrolled in the Ph.D. program aiming to conduct the fusion research in IIIS.

To enable the sustainable development of this Ph.D. program, it is important to secure financial resources that substitute for those being provided by the WISE Program in several years. We are thus preparing to set up the Collaboration Council as a portal for academic-industrial alliance. The council is expected to produce partnerships with companies in a wider range of sectors than those IIIS alone had made before. At the same time, we aim to further strengthen alliance with companies that are already conducting research collaboration by providing educational opportunities for human resources in companies.

The WISE Program's budget allows us to employ some faculty members contributing to the Ph.D. program and improve research facilities to be used for dissertation studies of the students, enhancing the education and research systems of IIIS and the university. Actually, personnel expenses of three young faculty members in IIIS are born by the Ph.D. program, and ¥169 M of equipment has been purchased for set-up/improve labs to be used for dissertation studies, contributing to IIIS significantly.

7. Center's Response to Results of Last Year's Follow-up

* Transcribe the item from the "Actions required and recommendations" section in the site visit report and the Follow-up report, then note how the center has responded to them.
* If you have already provided this information, indicate where in the report.

7-1. Center's Response to the site-visit report

(1) *While IIIS has produced several outstanding results, it seems that it has not exploited the potential that these results provide for further understanding of sleep; the role Sik3 plays in controlling sleep is an important case. Research conducted by junior PIs is interesting and promising, but some of it would seem to require deeper thought as to its relevance to understanding the essentials of sleep.*

We, of course, agree that the role of Sik3 in controlling sleep is very important. We are working on two main issues: SIK3-signaling pathway and neuronal groups responsible for the determination of sleep need. To elucidate the SIK3 pathway regulating sleep, we have been conducting biochemical approach using FLAG-tag knock-in mice and genetic approach such as suppressor screening of SIK3 mutant mice. We have done the sleep/wake analysis of mice with SIK1 S577A, SIK2 S587A and SIK3 S551A to confirm the PKA-SIK signaling as a common sleep need pathway. We are extending our analysis using mice with SIK3 T221A, SIK3 T469A and SIK3 S674A. Our systematic approaches using a variety of Cre-driver mice and locally delivered Cre or SIK3 using AAV have led us to narrow down to specific sets of neurons.

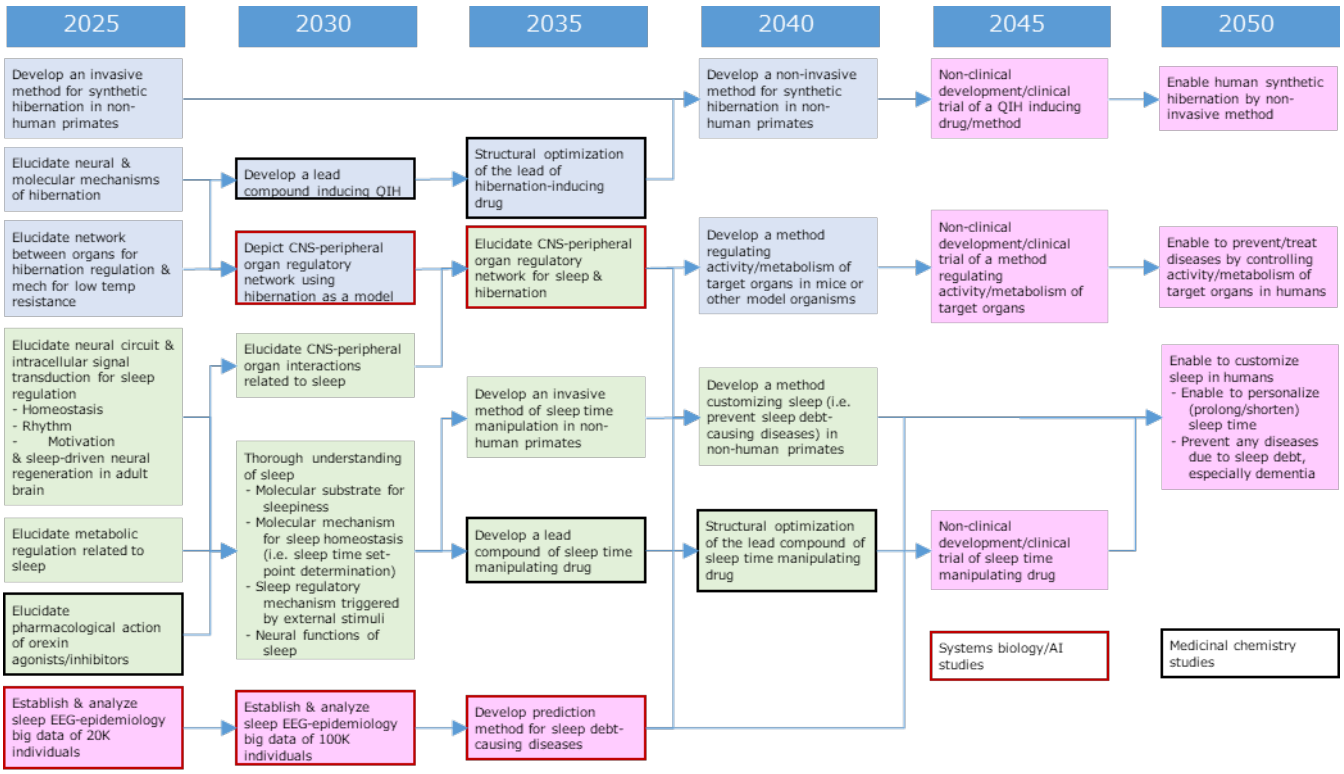
Following the advices in the site-visit and follow-up reports, we set forth long-term objectives of IIIS to be achieved by FY 2050, as shown in the following paragraph. As a major milestone at FY 2030, we aim to achieve thorough understanding of sleep, which involves sleep regulatory mechanisms triggered by external stimuli including pregnancy, innate fear, sexual behaviors, etc.

(2) *The center's progress plan is broadly challenging but quite open-ended, and its research on hibernation-like behavior is added almost like an afterthought. Given that University of Tsukuba pledges to provide 12 PI positions and secure additional funding, and given IIIS's excellent achievements and the buildup of its research capability, one would like to see a progress plan that spells out in much more concrete detail the center's research targets and its strategy for achieving them including the addition of new talents in the PI lineup replacing the ones leaving.*

We have realized that the 5 year term was too short for the WPI Center carrying out biological research such as IIIS to set forth clear objectives that could give big impacts on the society. The 5 year plan has no choice but to become open-ended, and we thus decided to set objectives to be achieved in 30 years and make a plan to implement the objectives and milestones as shown below.

As we discussed in 5-1., we decided to extend our research goal from "solving the mystery of sleep" to "solving the mysteries of hypomobile behaviors." Many behaviors of animal, *e.g.*, feeding, reproduction and aggressive behavior, are consisted of motions, while two hypomobile behaviors, sleep and hibernation are regulated hypomobile states essential for life support. Although no motions are involved in these behaviors, CNS-peripheral organ regulatory networks, as well as neural networks in CNS, are essential for both of the hypomobile behaviors. Through elucidation of these networks, we envisage enabling 3 objectives; 1) to customize sleep as we would like, 2) to realize human synthetic hibernation, 3) to prevent/treat diseases by controlling activity/metabolism of a target organ.

By customizing sleep, we may prolong or shorten sleeping time as we need/wish without any adverse effects. We could prevent any disease caused by sleep deprivation, especially dementia or neurodegenerative disease. Synthetic hibernation would enable an interplanetary space flight, as well as rescuing lives in emergency such as a big accident and/or health-care exigency including a pandemic like COVID-19. If we can control activity/metabolism of any peripheral organ in overload to avoid failure of homeostasis, we could prevent various disease.



According to the 30 year plan, we assumed 7 milestones to be marked by FY 2025, and we now plan to reorganize our network of satellites and on-campus collaboration significantly. We expect many changes in Satellite PIs and Collaborative PIs, while we would maintain the core group of IIIS mostly. We would recruit a few PIs as substitute to let 2 PIs retire.

(3) *Remarkable achievements by IIIS provide unique, novel targets for drug discovery, such as inhibitors or activators of Sik3 and agonists or antagonists for QRFP or the Q neurons. It is time for IIIS to start conducting assay development and high-throughput screening, which are necessary for drug discovery based on its new findings. It will be worthwhile to consider collaboration with some outside academic drug discovery programs to identify seed compounds, from which IIIS's strong medchem group can develop patentable new compounds as leads.*

We are not sure if SIK3 is a good drug target to regulate the sleep homeostasis due to its broad expression profile. There might be a better target molecule in the SIK3 pathway. We also know that QRFP is not involved in the signal transduction through the neural circuit as a neurotransmitter, and we try to find the relevant neurotransmitter and its receptor. As soon as we identify a good drug target, we will conduct the assay development and HTS in collaboration with Drug Discovery Initiative in Tokyo University or a pharmaceutical company.

(4) *Although the director would like to reorganize the center's human resources to focus more on basic sleep and to transfer the human research and medicinal chemistry divisions to another institute in University of Tsukuba, we feel that these divisions should belong to IIIS when its extension is permitted.*

Although the 5 year extension of IIIS was not granted, we have revised our future plan to be more aggressive as described above, and the core group of IIIS which includes the pharmaceutical science and experimental medicine groups should be maintained as it is.

(5) *IIIS should bear in mind the need to give further consideration to promoting diversity*

and to maintaining research integrity at various levels. At this moment, only two female PIs out of 20 (10%) are employed in the institute, while among the poster presenters at this site visit, half were female (more than 50%). Even though it is not possible to hire an equal percentage of female PIs, the gender ratio among speakers invited to IIIS seminars should be considered.

We continue the effort to hire more female PIs and to invite more female speakers to IIIS Seminars.

(6) *It would be desirable to have an additional program in systems biology or theoretical neuroscience that would inform the group to help them address fundamental questions in the organization of the neuronal/molecular systems associated with sleep regulation. It should be noted that theoretical contributions to experimental neuroscience are rare, and only successful when serious investments are made in recruiting teams of data scientists, computational neuroscientists and theoretical neuroscientists who maintain constant contact with the experimentalists. IIIS could constitute an ideal and unique environment for cross fertilization between sleep theory and experimental discovery.*

Following this advice, we plan to offer a full-time PI position next year to the computer scientist in CCS, with whom we collaborate in the development of automated sleep staging software based on deep learning models now. In addition to him, we would like to collaborate with 2 more system biologists/bioinformatics scientists on-campus and organize a virtual core function in IIIS, System Biology/AI Core, to elucidate neural networks as well as CNS-peripheral organ regulatory networks.

(7) *The new program in human sleep biology is very exciting if integrated into the structure of IIIS. The ability to conduct detailed studies of human sleep metabolism, sleep monitorization, mobile sleep lab is exciting and challenging, as it may lead to translation of basic science developed in the first 7 years of IIIS and the development of personalized therapeutic interventions. However, details on its implementation, including statistical power analysis, a strategy for candidate gene approach, expectations, milestones and alternative approaches were not fully developed.*

We agree that the development of human sleep biology in IIIS is still at its early stage. The completion of Human Sleep Lab, however, has given us a good foundation of the translational research to build up the human sleep biology. We continue efforts to expand our studies of human sleep physiology/experimental medicine, including the recruitment of 2 medical specialists in collaboration with the Hospital Management Division of Ibaraki Prefecture, the expansion of the human genetics in cooperation with Gui de Chauliac Hospital, and the construction of big data on sleep/epidemiology in collaboration with S'UIMIN Inc.

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

(1) *While IIIS has produced several outstanding results, it appears that it has not fully exploited the potential that these results provide for the further understanding of sleep. The role that Sik3 plays in controlling sleep is an important example.*

We, of course, agree that the role of Sik3 in controlling sleep is very important. We have thus performed several studies of the Sik3 pathway including neuron-specific Sik3 deficiency, PKA-SIK3 family analysis, and the phosphoproteomics in the Sleepy mutant mouse, and continue the study to identify SIK3 substrates.

(2) *Remarkable achievements by IIIS provide unique, novel targets for drug discovery, such as Sik3 inhibitors or activators and agonists or antagonists for Q neurons. It is time for IIIS to start conducting assay development and high throughput screening.*

We are not sure if SIK3 is a good drug target to regulate the sleep homeostasis due to its broad expression profile. There might be a better target molecule in the SIK3 pathway.

We also know that QRFP is not involved in the signal transduction through the neural circuit as a neurotransmitter, and we try to find the relevant neurotransmitter and its receptor. As soon as we identify a good drug target, we will conduct the assay development and HTS in collaboration with Drug Discovery Initiative in Tokyo University or a pharmaceutical company.

(3) *It would be desirable to have an additional program in systems biology or theoretical neuroscience. This would help IIIS address fundamental questions in the organization of the neuronal/molecular systems associated with sleep regulation.*

Following this advice, we plan to offer a full-time PI position next year to the computer scientist in CCS, with whom we collaborate in the development of automated sleep staging software based on deep learning models now. In addition to him, we would like to collaborate with 2 more system biologists/bioinformatics scientists on-campus and organize a virtual core function in IIIS, System Biology/AI Core, to elucidate neural networks as well as CNS-peripheral organ regulatory networks.

(4) *Although IIIS is indeed different and has created a novel research structure, it remains to be seen whether IIIS has broadly reformed the university.*

University of Tsukuba officially established Organization for Development of Global Research Centers, which is comprised of Center for Computational Sciences (CCS), Life Science Center for Survival Dynamics, Tsukuba Advanced Research Alliance (TARA-Center), and IIIS. The Organization aims to expand horizontally among these centers the tasks/achievements of promoting the advanced and interdisciplinary researches, internationalization, and reforming systems thus far headed by the IIIS. Much is expected of IIIS to contribute for the success of the Organization by the active sharing of experience, knowledge, and know-how accumulated at IIIS.

(5) *The director serves as the CEO of the venture S'UIMIN Inc. His role may pose a conflict of interest and of commitment, so will need to be monitored.*

The COO of S'UIMIN Inc., Fujiwara substituted for the CEO, and the Center Director was nominated to the Chairman of the Board/CSO in December, 2019. To avoid COI further, the Board of Directors has decided that the Center Director should not participate in any decisions on issues/deals/contracts with IIIS. In addition, the compliance committee at IIIS copes appropriately.

Appendix 1 FY 2019 List of Center's Research Results and Main Awards

1. Refereed Papers

- List only the Center's papers published in 2019. (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 "WPI" and the name of the WPI center (WPI-center name)). (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. From 2012, the authors' affiliations must be clearly noted.

(2) Method of listing paper
- List only refereed 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 consistent. (The names of the center researchers do not need to be underlined.)
- If a paper has many authors (say, more than 10), all of their names do not need to be listed.
- Assign a serial number to each paper to be used to identify it throughout the report.
- If the papers are written in languages other than English, underline their serial numbers.
- Order of Listing

A. WPI papers
1. Original articles
2. Review articles
3. Proceedings
4. Other English articles

B. WPI-related papers
1. Original articles
2. Review articles
3. Proceedings
4. Other English articles

(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.
- 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. Chang YH, Nishimura S, Oishi H, Kelly VP, Kuno A, Takahashi S (2019) TRMT2A is a novel cell cycle regulator that suppresses cell proliferation. *Biochem Biophys Res Commun* **508**(2): 410-415. doi:10.1016/j.bbrc.2018.11.104

2. Fujii S, Kaushik MK, Zhou XZ, Korkutata M, Lazarus M (2019) Acute social defeat stress increases sleep in mice. *Front Neurosci* **13**. doi:10.3389/fnins.2019.00322

3. Fujimori K, Aritake K, Oishi Y, Nagata N, Maehara T, Lazarus M, Urade Y (2019) L-PGDS-produced PGD(2) in premature, but not in mature, adipocytes increases obesity and insulin resistance. *Sci Rep* **9**. doi:10.1038/s41598-018-38453-y

4. Furuse T, Mizuma H, Hirose Y, Kushida T, Yamada I, Miura I, Masuya H, Funato H, *et al.* (2019) A new mouse model of GLUT1 deficiency syndrome exhibits abnormal sleep-wake patterns and alterations of glucose kinetics in the brain. *Dis Model Mech* **12**(9). doi:10.1242/dmm.038828

5. Hada K, Hirota K, Inanobe A, Kako K, Miyata M, Araoi S, Matsumoto M, Ohta R, *et al.* (2019) Tricarboxylic acid cycle activity suppresses acetylation of mitochondrial proteins during early embryonic development in Caenorhabditis elegans. *J Biol Chem* **294**(9): 3091-3099. doi:10.1074/jbc.RA118.004726

6. Hori D, Oi Y, Ohtaki Y, Andrea CS, Takahashi T, Shiraki N, Ikeda T, Ikeda Y, *et al.* (2019) Association between flourishing mental health and occupational stress among workers of Tsukuba Science City, Japan: a cross-sectional study. *Environ Health Prev* **24**(1). doi:10.1186/s12199-019-0823-7

7. Hori D, Takao S, Kawachi I, Ohtaki Y, Andrea CS, Takahashi T, Shiraki N, Ikeda T, *et al.* (2019) Relationship between workplace social capital and suicidal ideation in the past year among employees in Japan: a cross-sectional study. *BMC Public Health* **19**. doi:10.1186/s12889-019-7244-9

8. Imanishi A, Kanbayashi T, Sagawa Y, Taniguchi T, Usumoto A, Yuge K, Kotorii N, Kinoshita T, *et al.* (2019) Normal CSF orexin levels in the patients with hypersomnolence following HPV vaccination. *Sleep Biol Rhythms* **17**(2): 259-261. doi:10.1007/s41105-019-00210-7

9. Kakizaki M, Tsuneoka Y, Takase K, Kim SJ, Choi J, Ikkyu A, Abe M, Sakimura K, Yanagisawa M, Funato H (2019) Differential roles of each orexin receptor signaling in obesity. *iScience* 20: 1-13. doi:10.1016/j.isci.2019.09.003

10. Kanemaru K, Noguchi E, Tahara-Hanaoka S, Mizuno S, Tateno H, Denda-Nagai K, Irimura T, Matsuda H, *et al.* (2019) Clec10a regulates mite-induced dermatitis. Sci Immunol 4(42). doi:10.1126/sciimmunol.aax6908

11. Kawai H, Takaki M, Sakamoto S, Shibata T, Tsuchida A, Yoshimura B, Yada Y, Matsumoto N, *et al.* (2019) Anti-NMDA-receptor antibody in initial diagnosis of mood disorder. *Eur Neuropsychopharmacol* **29**(9): 1041-1050. doi:10.1016/j.euroneuro.2019.07.137

12. Kitamura S, Takahashi M, Mishima K (2019) Sleep problem but not chronotype is associated with retirement from shift work: a cross-sectional retrospective study. *Sleep Biol Rhythms* **17**(3): 331-337. doi:10.1007/s41105-019-00221-4

13. Kodani S, Soya S, Sakurai T (2019) Optogenetic manipulation of neural circuits during monitoring sleep/wakefulness states in mice. *J Vis Exp* (148). doi:10.3791/58613

14. Korkutata M, Saitoh T, Cherasse Y, Ioka S, Duo F, Qin RJ, Murakoshi N, Fujii S, *et al.* (2019) Enhancing endogenous adenosine A(2A) receptor signaling induces slow-wave sleep without affecting body temperature and cardiovascular function. *Neuropharmacology* **144**: 122-132. doi:10.1016/j.neuropharm.2018.10.022

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16. Kutsumura N, Numata K, Mosaki S, Saito T (2019) Total synthesis of haplacutines B and C. *Heterocycles* **99**(1): 614-624. doi:10.3987/COM-18-S(F)7

17. Lu WZ, Kim JD, Tabara S, Kwon C, Mizukami H, Kimura K, Fukamizu A (2019) The N-terminal sequence of murine PRMT5 variant 2 is required for Hsp70 interaction and CHIP ligase-mediated degradation. *Biochem Biophys Res Commun* **514**(4): 1185-1191. doi:10.1016/j.bbrc.2019.05.077

18. Matsubara T, Suzuki K, Kawasaki A, Miyamoto M, Okamura M, Kanbayashi T, Takekawa H, Nakamura T, *et al.* (2019) Sudden onset of sleep caused by hypothalamic infarction: a case report. *BMC Neurol* **19**(1). doi:10.1186/s12883-019-1414-3

19. Miyagawa T, Hida A, Shimada M, Uehara C, Nishino Y, Kadotani H, Uchiyama M, Ebisawa T, *et al.* (2019) A missense variant in PER2 is associated with delayed sleep-wake phase disorder in a Japanese

population. *J Hum Genet* **64**(12): 1219-1225. doi:10.1038/s10038-019-0665-6

20. Miyoshi C, Kim SJ, Ezaki T, Ikkyu A, Hotta-Hirashima N, Kanno S, Kakizaki M, Yamada M, *et al.* (2019) Methodology and theoretical basis of forward genetic screening for sleep/wakefulness in mice. *Proc Natl Acad Sci U.S.A.* **116**(32): 16062-16067. doi:10.1073/pnas.1906774116

21. Mizukami H, Kim JD, Tabara S, Lu WZ, Kwon C, Nakashima M, Fukamizu A (2019) KDM5D-mediated H3K4 demethylation is required for sexually dimorphic gene expression in mouse embryonic fibroblasts. *J Biochem* **165**(4): 335-342. doi:10.1093/jb/mvy106

22. Morita E, Kadomatsu Y, Tsukamoto M, Kubo Y, Okada R, Sasakabe T, Kawai S, Hishida A, Naito M, Wakai K (2019) Frequency of forest walking is not associated with prevalence of hypertension based on cross-sectional studies of a general Japanese population: a reconfirmation by the J-MICC Daiko Study. *Nagoya J Med Sci* **81**(3): 489-500. doi:10.18999/nagjms.81.3.489

23. Nagano K, Kwon C, Ishida J, Hashimoto T, Kim JD, Kishikawa N, Murao M, Kimura K, *et al.* (2019) Cooperative action of APJ and alpha 1A-adrenergic receptor in vascular smooth muscle cells induces vasoconstriction. *J Biochem* **166**(5): 383-392. doi:10.1093/jb/mvz071

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Curr Biol **29**(4): 637-644. doi:10.1016/j.cub.2018.12.031

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(2) Review Articles

48. Barton M, Yanagisawa M (2019) Endothelin: 30 years from discovery to therapy. *Hypertension* **74**(6): 1232-1265. doi:10.1161/HYPERTENSIONAHA.119.12105

49. Fifel K, Videnovic A (2019) Chronotherapies for Parkinson's disease. *Prog Neurobiol* **174**: 16-27. doi:10.1016/j.pneurobio.2019.01.002

50. Kako K, Kim JD, Fukamizu A (2019) Emerging impacts of biological methylation on genetic information. *J Biochem* **165**(1): 9-18. doi:10.1093/jb/mvy075

51. Koyanagi I, Akers KG, Vergara P, Srinivasan S, Sakurai T, Sakaguchi M (2019) Memory consolidation during sleep and adult hippocampal neurogenesis. *Neural Regen Res* **14**(1): 20-23. doi:10.4103/1673-5374.243695

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(3) Proceedings

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(4) Other English Articles

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WPI-related papers

(1) Original articles

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98. Green CB (2019) Many paths to preserve the body clock. *Science* **363**(6423): 124-125. doi:10.1126/science.aav9706

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

- List up to 10 main presentations during FY 2019 in order from most recent.
- For each, write the date(s), lecturer/presenter's name, presentation title, and conference name.

Date(s)	Lecturer/Presenter's name	Presentation title	Conference name
Dec 4	Takeshi Sakurai	Keynote Lecture: Neural circuits that link the limbic system and systems that regulate arousal	IRC* Decoding Sleep Symposium (Bern, Switzerland)
Oct 23	Hiroshi Nagase	Opening Lecture: Design and synthesis of orexin receptor selective ligands and their pharmacology	Novel Pain Therapeutics: From Basic Research to Clinical Translation and Rehabilitation (Rende (Cosenza), Italy)
Sep 24	Masashi Yanagisawa	Keynote Lecture: Toward the mysteries of sleep	World Sleep 2019 (Vancouver, Canada)
Sep 24	Michael Lazarus	Symposium: The gating and maintenance of sleep and wake: New circuits and insights	The 10th IBRO World Congress of Neuroscience (Daegu, Korea)
Sep 22	Masanori Sakaguchi	Symposium: Mechanism of memory engram	
Sep 14	Takeshi Sakurai	Keynote Lecture: The neuronal circuitry of narcolepsy/cataplexy	Workshop on Sleep Regulation and Circadian Rhythms (Beijing, China)
Aug 26	Yu Hayashi	Identifications of neurons regulating REM sleep & insights to the mechanisms of REM sleep behavior disorder	XVI Congress of the European Biological Rhythms Society (Lyon, France)
May 19	Masashi Yanagisawa	Keynote Lecture: Toward the mysteries of sleep	10th European Narcolepsy Day (Bern, Switzerland)

Apr 27	Hiromasa Funato	Forward genetics in mice identified novel sleep-regulating genes	V World Congress of Chronobiology (Suzhou, China)
Apr 25	Qinghua Liu	Quantitative phosphoproteomic analysis of the molecular substrates of homeostatic sleep need	

3. Major Awards

- List up to 10 main awards received during FY 2019 in order from the most recent.
- For each, write the date issued, the recipient's name, and the name of award.
- In case of multiple recipients, underline those affiliated with the center.

Date	Recipient's name	Name of award
Jan 25	Shingo Soya	Excellent Poster Award (The 10th Takeda Science Foundation Symposium on Pharma Sciences)
Dec 19	Shingo Soya Ai Miyasaka	Presentation of Young Scientist Award (Next Generation Brain Project Winter Symposium 2019)
Nov 14	Tsuyoshi Saitoh	Reaction Chemistry & Engineering Poster Prize (SelectBIO Flow Chemistry Asia 2019)
Nov 6	Masashi Yanagisawa	Ibaraki Prefecture Honor Award
Oct 29	Masashi Yanagisawa	Person of Cultural Merit
Aug 2	Yu Hayashi	Special Prize, The Frontier Salon Nagase Prize
Jun 22	Asuka Ishihara	Best Poster Presentation Award (31st Annual Meeting of Light Treatment and Biological Rhythms)
Jun 21	Masashi Yanagisawa	Takamine Memorial Daiichi Sankyo Prize
May 27	Yuki Saito	Encouraging Prize of Japanese Society for Sleep Research
May 18	Masashi Yanagisawa	European Narcolepsy Research Award

Appendix 2 FY 2019 List of Principal Investigators

NOTE:

*Underline names of principal investigators who belong to an overseas research institution.

*In the case of researcher(s) not listed in the latest report or, for centers selected in FY2012 in the progress report for Extension application screening, attach a "Biographical Sketch of a New Principal Investigator" (Appendix 2a).

<Results at the end of FY2019> **Principal Investigators Total: 29**

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	59	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	55	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba; Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D.; Neuroscience	80	April 2013	Usually stays at the center	
Hiromasa Funato	50	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba Associate Professor, Toho University	M.D., Ph.D.; Neuroscience	40	December 2012	Usually stays at the center three times a week	
Robert Greene	69	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 Zoom) 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 the transriptomic changes induced by homeostatic sleep
Qinghua Liu	48	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba, Japan; Investigator, National Institute of Biological Sciences (NIBS), Tsinghua University, China;	Ph.D. ; Genetics, Molecular Biology, Biochemistry	10	April 2013	a) Stays at the center for 1 month/year; site visit, symposium b) Joins a videoconference from abroad >1x /week c) attends (by Skype) PI meeting 1X/month	Accept young scientists to WPI center (1/period)
Hiroshi Nagase	72	Specially Appointed Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D.; Medicinal Chemistry, Organic Chemistry	65	April 2013	Usually stays at the center	
Noriki Kutsumura	42	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D.; Organic Chemistry, Medicinal Chemistry	80	April 2013	Usually stays at the center	
Makoto Satoh	64	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D.; Sleep Medicine	65	April 2015	Usually stays at the center	
Kumpei Tokuyama	66	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D., ; Energy Metabolims	80	April 2015	Usually stays at the center	
Takashi Kanbayashi	56	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba; Physician, Ibaraki Prefectural Medical Center of Psychiatry	M.D., Ph.D.; Sleep Medicine and Psychiatry	80	April 2019	Stays 2 days at IIIS and 3 days at the satellite center	
Ichiyo Matsuzaki	60	Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. ; Occupational Psychiatric Medicine, Space Medicine	10	March 2013	About 10% of effort. The remaining is allocated for Faculty of Medicine.	
Hitoshi Shimano	60	Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. ; Endocrinology, Metabolism	15	March 2013	Usually stays at Faculty of Medicine	
Akiyoshi Fukamizu	60	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	58	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	68	Professor, Department of Neuroscience, University of Texas Southwestern Medical Center Investigator, Howard Hughes Medical Institute	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	57	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	52	Professor, Department of Molecular and Cell Biology, University of California, Berkeley	Ph.D.; Neurobiology	5	April 2014	Usually stays at the satellite center	Occasional consultation
Hitoshi Okamura	67	Professor, Graduate School of Pharmaceutical Sciences, Kyoto University	M.D., Ph.D.; Chronobiology	3	July 2015	Usually stays at the satellite center Participates in annual Site Visit	
Kazuo Mishima	57	Professor, Department of Neuropsychiatry, Akita University Graduate School of Medicine	M.D., Ph.D.; Medical Science	5	October 2018	Usually stays at the satellite center	
Kaspar Vogt	53	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	50	Associate Professor International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D.; Neuroscience	100	April 2013	Usually stays at the center	
Masanori Sakaguchi	43	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	39	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D.; Neuroscience	100	April 2013	Usually stays at the center	
Takashi Abe	40	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D.; Behavioral Science Psychophysiology	100	November 2017	Usually stays at the center	
Sakiko Honjoh	39	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	
Yo Oishi	39	Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D.; Neuroscience	100	April 2013	Usually stays at the center	
Katsuyasu Sakurai	41	Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D.; Neuroscience	100	July 2017	Usually stays at the center	
Arisa Hirano	34	Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba; Assistant Professor, Faculty of Medicine, University of Tsukuba	Ph.D.; Molecular biology, Genetics, Neuroscience	80	April 2019	Usually stays at the center	
Hirofumi Toda	41	Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D.; Genetics	50	July 2019	Usually stay at the center	

*Percentage of time that the principal investigator devotes to working for the center vis-à-vis his/her total working hours.

Principal investigators unable to participate in project in FY 2019

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age)

Arisa Hirano (34)

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

Assistant Professor, Faculty of Medicine/WPI-IIIS, University of Tsukuba

Academic degree and specialty

Ph.D.; Molecular biology, Genetics, Neuroscience

Effort **80 %**

* Percentage of time that the principal investigator devotes to working for the center vis-à-vis his/her total working hours.

Research and education history

Education

2008.3 B.S. Department of biophysics and biochemistry, School of Science, The University of Tokyo, Japan

2010.3 M.S. Department of biophysics and biochemistry, Graduate School of Science, The University of Tokyo, Japan

Research project: Molecular mechanism of the circadian clock

2013.3 Ph.D. Department of biophysics and biochemistry, Graduate School of Science, The University of Tokyo, Japan (Supervisor; Dr. Yoshitaka Fukada)

Research project: Molecular mechanism of the circadian clock

Employment

2019.4-present Assistant professor and Principal investigator, Faculty of Medicine, University of Tsukuba

Research project: Molecular and neural mechanism of the circadian rhythms

2019.4-present Assistant professor and Principal investigator, WPI-IIIS, University of Tsukuba

2017.4-2019.3 Assistant professor, WPI-IIIS, University of Tsukuba

Research project: Molecular and neural mechanism of the circadian rhythms

2014.4-2017.3 Postdoctoral fellow, University of California, San Francisco, USA

Research project: Molecular characterization of human sleep disorder

2013.4-2014.3 Project assistant professor, Department of biophysics and biochemistry, Graduate School of Science, The University of Tokyo, Japan

Research project: Molecular mechanism of the circadian clock

Achievements and highlights of past research activities

She is aiming to understand how the circadian rhythms including sleep/wake cycle are tightly regulated. First, she demonstrated the molecular mechanism of clock protein regulation by posttranslational modifications (Hirano et al., Cell, 2013 etc.). Ubiquitination as well as phosphorylation have an essential role in the molecular oscillation and behavioral rhythms in mice. In her postdoctoral training, she utilized human genetics and revealed the molecular mechanism of human sleep disorder. She identified several mutations in clock genes altering schedule of sleep/wake cycle and showed the impact of these mutation on the protein function and the circadian clock system (Zhang, Hirano et al., PNAS, 2016; Hirano et al., eLIFE, 2016, etc.). Her findings enhanced our understanding of the circadian clock especially at the molecular level. Currently, she is trying to understand the circadian clock at the systems level focusing on input and output pathways. She has already obtained the research results indicating important neural pathways regulating sleep/wake regulation (Hirano et al., in preparation).

Achievements

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

a) Recipient of international awards

2012 SRBR (Society for research on biological rhythms, USA) trainee awards

b) Member of a scholarly academy in a major country

N/A

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

2020.5 2020 SRBR meeting, invited speaker (will be online meeting due to the pandemic of COVID-19)

2021.7 Asia Forum on Chronobiology, invited speaker (2020 meeting was postponed due to the pandemic of COVID-19)

d) Editor of an international academic journal

N/A

e) Peer reviewer for an overseas competitive research program (etc.)

2018, referee of Frontiers Neuroscience

2018, referee of Scientific reports

2019, referee of Journal of Human Genetics

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

2019.4-2022.9 JST PRESTO (40 million yen/3.5 years)

2017 Inoue Research Awards (5 million yean/2 years)

(3) Major publications (Titles of major publications, year of publication, journal

name, number of citations)

Hirano A, Pei-Ken Hsu, Zhang L, Xing L, McMahon T, Yamazaki M, Ptáček L, Fu Y. DEC2 modulates orexin expression and regulates sleep. *Proc Natl Acad Sci* U S A., **115**, 3434-3439, 2018

Hayasaka N, **Hirano A**, Miyoshi Y, Tokuda IT, Yoshitane H, Matsuda J, Fukada Y. Salt-inducible kinase 3 regulates the mammalian circadian clock by destabilizing PER2 protein. *eLife*, **6**, e24779, 2017

Hirano A, Braas D, Fu Y, Ptáček L. FAD regulates CRYPTOCHROME protein stability and circadian clock in mice. *Cell Reports*, **19**, 255-266, 2017

Hirano A, Shi G, Jones C , Lipzen A, Pennacchio L, Xu Y, Hallows W, McMahon T, Yamazaki M, Ptáček L, Fu Y. A Cryptochrome 2 Mutation Yields Advanced Sleep Phase in Humans. *eLife*, **5**, e16695, 2016

Hirano A, Fu Y, Ptáček L. The intricate dance of post-translation modifications in the rhythm of life. *Nat. Struct. Mol. Biol.*, **23**, 1053-1060, 2016 (review)

Hirano A[#], Nakagawa T[#], Yoshitane H, kozuka-Hata H, Oyama M, Lanjacornsiripan D, Fukada Y. USP7 and TDP-43: Pleiotropic regulation of Cryptochrome protein stability paces the oscillation of the mammalian circadian clock. *PLOS ONE*, **11**, e0154263. (# Co-first author), 2016

Zhang L[#], **Hirano A**[#], Hsu P, Jones C, Sakai N, Okuro M, McMahon T, Yamazaki M, Xu Y, Saigoh N, Saigoh K, Lin S, Kaasik K, Nishino S, Ptáček L, Fu Y. A PERIOD 3 variant causes a circadian phenotype and is associated with a seasonal mood trait. *Proc Natl Acad Sci* U S A. **113**, E1536-1544, (# Co-first author), 2016,

Shen Y, Ge WP, Li Y, **Hirano A,** Lee HY, Rohlmann A, Missler M, Tsien RW, Jan LY, Fu YH, Ptáček LJ. Protein mutated in paroxysmal dyskinesia interacts with the active zone protein RIM and suppresses synaptic vesicle exocytosis. *Proc Natl Acad Sci* U S A. **112**, 2935-2941, 2015

Hirano A, Kurabayashi N, Nakagawa T, Shioi G, Todo T, Hirota T, Fukada Y. *In vivo* role of phosphorylation of Cryptochrome 2 in the mouse circadian clock. *Mol Cell Biol.* **34**, 4464-73., 2014

Hirano A, Yumimoto K, Tsunematsu R, Matsumoto M, Oyama M, Kozuka-Hata H, Nakagawa T, Lanjakornsiripan D, Nakayama KI, and Fukada Y. FBXL21 Regulates Oscillation of the Circadian Clock through Ubiquitination and Stabilization of Cryptochromes. *Cell*, **152**, 1106-1118, 2013

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

N/A

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age) Takashi Kanbayashi (56)

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

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

Academic degree and specialty

Akita University School of Medicine, Akita, Japan	Ph.D.	1998	Neuroscience, Sleep, Pharmacology, Psychiatry
Akita University School of Medicine, Akita, Japan	M.D.	1990	Medicine

Effort 80 %

* Percentage of time that the principal investigator devotes to working for the center vis-à-vis his/her total working hours.

Research and education history

1990-1992 Resident in Neuropsychiatry, Akita University School of Medicine
1992-1998 Ph.D. program, Akita University School of Medicine
1994-1996 Post-doctoral Research Fellow, Stanford University School of Medicine.
1998-2006 Assistant Professor, Akita University School of Medicine
2006-2019 Associate Professor, Akita University School of Medicine
2019-present Professor, WPI-IIIS, University of Tsukuba

Achievements and highlights of past research activities

His research field is to measure orexin for a definitive diagnosis of narcolepsy. He found low orexin levels in cerebrospinal fluid from patients suffering from multiple sclerosis, brain tumors, and hereditary disorders with symptomatic narcolepsy, and performed a meta-analysis of 150 cases in combination with past cases. To date, more than 3000 samples have been measured for CSF orexin. He continues to provide diagnosis and treatment advices to the medical doctors who sent the samples.

2016 Award of Hishikawa foundation
2013 Award of Japanese Society for Hydrocephalus and CSF Disorders
2013 Award of Research Group of Schizophrenia
2006 Award of Hishikawa foundation

Achievements

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

a) Recipient of international awards (-)

b) Member of a scholarly academy in a major country (-)

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

Kanbayashi T. Neuro-immune diseases in symptomatic narcolepsy 1st Asian Narcolepsy & Hypersomnolence Society Meeting Seoul 2017

Kanbayashi T. Symptomatic Narcolepsy among Children and Adolescence, Such as Niemann-Pick Type C and Prader-Willi Syndrome The 4th International Pediatric Sleep Association Congress In conjunction with The 14th Annual Meeting of Taiwan Society of Sleep Medicine, Taipei 2016

Kanbayashi T. Symptomatic narcolepsy among inherited disorders, such as Niemann-Pick type C, Prader-Willi syndrome and Myotonic dystrophy type 1 6th World Congress on Sleep Medicine, Seoul 2015

Kanbayashi T. Anti-NMDA-receptor antibodies detected in limbic encephalitis, schizophrenia and narcolepsy with psychotic symptoms 9th International Conference on Early Psychosis, Tokyo 2014

Kanbayashi T. Anti-NMDA-receptor antibody detected in limbic encephalitis, schizophrenia and narcolepsy with psychotic symptoms 4th Schizophrenia International Research Society Conference Florence 2014

d) Editor of an international academic journal (-)

e) Peer reviewer for an overseas competitive research program (etc.) (-)

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

Japan Agency for Medical Research and Development, Strategic Research Program for Brain Sciences,

“An attempt to improve the symptoms of dementia by improving sleep quality”

¥ 22,100,000 (11/1/2016 - 3/31/2021)

(3) Major publications (Titles of major publications, year of publication, journal name, number of citations)

Shimizu S, Takenoshita N, Inagawa Y, Tsugawa A, Hirose D, Kaneko Y, Ogawa Y, Serisawa S, Sakurai S, Hirao K, Kanetaka H, Kanbayashi T, Imanishi A, Sakurai H, Hanyu H. Positive Association Between Cognitive Function and Cerebrospinal Fluid Orexin A Levels in Alzheimer's Disease. J Alzheimers Dis. 2020;73 (1):117-123.

Kawai H, Takaki M, Sakamoto S, Shibata T, Tsuchida A, Yoshimura B, Yada Y, Matsumoto N, Sato K, Abe K, Okahisa Y, Kishi Y, Takao S, Tsutsui K, Kanbayashi T, Tanaka K, Yamada N. Anti-NMDA-receptor antibody in initial diagnosis of mood disorder. Eur Neuropsychopharmacol. 2019 Sep;29 (9):1041-1050. 2 citations

Omori Y, Kanbayashi T, Sagawa Y, Imanishi A, Tsutsui K, Takahashi Y, Takeshima M, Takaki M, Nishino S, Shimizu T. Low dose of aripiprazole advanced sleep rhythm and reduced nocturnal sleep time in the patients with delayed sleep phase syndrome: an open-labeled clinical observation. Neuropsychiatr Dis Treat. 2018 May 18;14:1281-1286. 4 citations

Omori Y, Kanbayashi T, Imanishi A, Tsutsui K, Sagawa Y, Kikuchi YS, Takeshima M, Yoshizawa K, Uemura S, Shimizu T. Orexin/hypocretin levels in the cerebrospinal fluid and characteristics of patients with myotonic dystrophy type 1 with excessive daytime sleepiness. Neuropsychiatr Dis Treat. 2018 Feb 8;14:451-457. 7 citations

Suzuki K, Miyamoto T, Miyamoto M, Maeda H, Nokura K, Tohyama J, Hirata K, Shimizu T, Kanbayashi T. Hypocretin-1 levels in the cerebrospinal fluid of patients with Percheron artery infarction with or without midbrain involvement: A case series. Medicine (Baltimore). 2016 Jul;95 (29):e4281. 8 citations

Omokawa M, Ayabe T, Nagai T, Imanishi A, Omokawa A, Nishino S, Sagawa Y, Shimizu T, Kanbayashi T. Decline of CSF orexin (hypocretin) levels in Prader-Willi syndrome. Am J Med Genet A. 2016 May;170A (5):1181-6. 12 citations

Kondo H, Ozone M, Ohki N, Sagawa Y, Yamamichi K, Fukuju M, Yoshida T, Nishi C, Kawasaki A, Mori K, Kanbayashi T, Izumi M, Hishikawa Y, Nishino S, Shimizu T Association between heart rate variability, blood pressure and autonomic activity in cyclic alternating pattern during sleep Sleep 37(1): 187-94 2014 17 citations

Suzuki K, Nakamura T, Hashimoto K, Miyamoto M, Komagamine T, Nagashima T, Izawa N, Kanbayashi T, Takahashi T, Hirata K. Hypothermia, hypotension, hypersomnia, and obesity associated with hypothalamic lesions in a patient positive for the anti-aquaporin 4 antibody: a case report and literature review. Arch Neurol. 69(10): 1355-9. 2012 50 citations

Kanbayashi T, Shimohata T, Nakashima I, Yaguchi H, Yabe I, Nishizawa M, Shimizu T, Nishino S. Symptomatic narcolepsy in patients with neuromyelitis optica and multiple sclerosis: new neurochemical and immunological implications. Arch Neurol 66(12): 1563-6. 2009 90 citations

Kanbayashi T, Kodama T, Kondo H, Satoh S, Inoue Y, Chiba S, Shimizu T, Nishino S. CSF histamine contents in narcolepsy, idiopathic hypersomnia and obstructive sleep apnea syndrome. Sleep 32(2): 181-7. 2009 128 citations

Oka Y, Inoue Y, Kanbayashi T, Kuroda K, Miyamoto M, Miyamoto T, Ikeda A, Shimizu T, Hishikawa Y, Shibasaki H. Narcolepsy without cataplexy: 2 subtypes based on CSF hypocretin-1/orexin-A findings. Sleep. 29(11): 1439-43 2006 47 citations

Nishino S, Kanbayashi T Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. Sleep Med Rev.9(4): 269-310. 2005 307 citations

Nishino S, Kanbayashi T, Fujiki N, Uchino M, Ripley B, Watanabe M, Lammers GJ, Ishiguro H, Shoji S, Nishida Y, Overeem S, Toyoshima I, Yoshida Y, Shimizu T, Taheri S, Mignot E. CSF hypocretin levels in Guillain-Barré syndrome and other inflammatory neuropathies. Neurology. 61(6): 823-5. 2003 92 citations

Kanbayashi T, Yano T, Ishiguro H, Kawanishi K, Chiba S, Aizawa R, Sawaishi Y, Hirota K, Nishino S, Shimizu T. Hypocretin-1 (orexin-A) levels in human lumbar CSF in different age groups: infants to elderly persons. Sleep 25(3): 337-9 2003 72 citations

Ogawa Y, Kanbayashi T, Saito Y, Takahashi Y, Kitajima T, Takahashi K, Hishikawa Y, Shimizu T. "Total sleep deprivation elevates blood pressure through arterial baroreflex resetting: a study with microneurographic technique. " Sleep 26(8): 986-9. 2003 211 citations

Kanbayashi T, Inoue Y, Chiba S, Aizawa R, Saito Y, Tsukamoto H, Fujii Y, Nishino S, Shimizu T. CSF hypocretin-1 (orexin-A) concentrations in narcolepsy with and without cataplexy and idiopathic hypersomnia. J Sleep Res. 11(1): 91-3. 2002 191 citations

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

Review Committee member of Hypersomnolence field for "The International Classification of Sleep Disorders, 2nd edition" (ICSD-2)

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age) : Noriki Kutsumura (42)

Affiliation and position: Professor (Co-PI), WPI-IIIS
Graduate School: Chemistry (main), Medical Sciences (sub), Life Science Innovation (Drug Discovery) (sub), Ph.D. Program in Humanics (sub)

Academic degree and specialty: Ph.D. (Sci.); Organic Chemistry, Medicinal Chemistry

Effort: 80%

Research and education history

Education history:

Apr. 1997–Mar. 2001. Undergraduate Student (Department of Chemistry, Keio University)

Apr. 2001–Mar. 2006. Graduate Student (School of Fundamental Science and Technology, Keio University)

* Mar. 2006, I received Ph.D. (Sci) from Keio University

Research history:

Apr. 2003–Mar. 2006. Researcher of "The 21st Century Center of Excellence Program of Japan", Keio University Life Conjugate Chemistry

Apr. 2006–Mar. 2007. Assistant Professor of Chemistry Class, Faculty of Law, Keio University

Apr. 2007–Mar. 2009. Pos-Doc Researcher of Chemistry Department, The University of Pennsylvania (USA)

Apr. 2009–Mar. 2013. Assistant Professor of Chemistry Department, Tokyo University of Science (TUS)

Apr. 2013–Jun. 2019. Associate Professor of WPI-IIIS, University of Tsukuba

Jul. 2019– Professor (Co-PI of Nagase/Kutsumura Lab.) of WPI-IIIS, University of Tsukuba

Apr. 2014–Mar. 2019, Apr. 2020– Lecturer of Chemistry Department, TUS

Achievements and highlights of past research activities

His research background is total synthesis of biologically active and structurally interesting natural products. He has achieved synthesis of about 20 natural products so far. He has also successfully developed a unique chemo- and stereoselective elimination reaction schemes that have been widely applied by organic chemists in the world. In addition, he has also published numerous papers in the field of heterocyclic chemistry. He is currently involved in drug discovery research using his outstanding organic synthetic technologies which he has mastered. His main research goal is to develop orexin receptor selective ligands, especially orexin 2 receptor

agonists. He reported the first syntheses of non-peptide selective orexin 2 receptor agonist YNT-185 in 2015 and potent and highly selective orexin 1 receptor antagonist YNT-1310 in 2017. In addition, he works on creation of not only orexin receptor ligands but also opioid receptor selective ligands and infectious antiprotozoal drugs.

Achievements

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

a) Recipient of international awards

- Highly Read Article of 2015 in Journal of Medicinal Chemistry (2017)
  "Design and Synthesis of Non-Peptide, Selective Orexin Receptor 2 Agonists"
  J. Med. Chem. **2015**, *58*, 7931-7937. (as a 3rd author)
- Highlighted paper selected by Editor-in-Chief and Featured Article (2019)
  "Total Synthesis of 3-*epi*-Juruenolide C"
  Chem. Pharm Bull. **2019**, *67*, 594-598. (as a 1st and the corresponding author)

b) Member of a scholarly academy in a major country

- Director of Electro Organic Chemistry (2013–)
- Director of The Chemical Society of Japan Kanto Branch (2017–)
- Director of The Pharmaceutical Society of Japan Kanto Branch (2019–)

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

Invited Lecture at 10th International Symposium on Organic Reactions (ISOR 10) in Yokohama
"Regioselective HBr-Elimination of Vicinal Dibromides Having an Adjacent *O*-Functional Group"

d) Editor of an international academic journal

none

e) Peer reviewer for an overseas competitive research program (etc.)

none

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

2019, The Ichiro Kanehara Foundation for the Promotion of Medical Sciences and Medical Care
500,000 Yen (1 year as a PI)

2019, JSPS, Grand-in-Aid for Scientific Research (C)
4,290,000 Yen (3 years as a PI)

2018, Terumo Life Science Foundation
2,000,000 Yen (1 year as a PI)

2017, JSPS, Grant-in-Aid for Young Scientists (B)
4,030,000 Yen (2 years as a PI)

2015, JSPS, Grant-in-Aid for Young Scientists (B)
3,900,000 Yen (2 years as a PI)

(3) Major publications (Titles of major publications, year of publication, journal name, number of citations) (update 10th March 2020)

1. "Structure-Activity Relationship between Thiol Group-Trapping Ability of Morphinan Compounds with a Michael Acceptor and Anti-*Plasmodium falciparum* Activities", **2020**, *Molecules*, 0.
2. "Total Synthesis of 3-*epi*-Juruenolide C", **2019**, *Chem. Pharm. Bull.*, 0.
3. "Farvorskii-Type Rearrangement of the 4,5-Epoxymorphinan Skeleton", **2018**, *Org. Lett.*, 3.
4. "The application of a specific morphinan template to the synthesis of galanthamine", **2017**, *Tetrahedron*, 7.
5. "Design and Synthesis of Potent and Highly Selective Orexin 1 Receptor Antagonists with a Morphinan Skeleton and Their Pharmacologies", **2017**, *J. Med. Chem.*, 14.
6. "Design and Synthesis of Non-Peptide, Selective Orexin Receptor 2 Agonists", **2015**, *J. Med. Chem.*, 42.
7. "Lewis Acid-Catalyzed or Base-Promoted Regioselective Cycloisomerization of *N*-Imidoyl-*o*-alkynylanilines for Synthesis of *N*-Imidoyl-(1*H*)-indoles and 4-Alkylidene-3,4-dihydroquinazolines", **2015**, *Adv. Synth. Catal.*, 17.
8. "Triflic acid-promoted cycloisomerization of 2-alkynylphenyl isothiocyanates and isocyanates: a novel synthetic method for a variety of indole derivatives", **2014**, *Org. Biomol. Chem.*, 14.
9. "One-Pot Method for Regioselective Bromination and Sequential Carbon-Carbon Bond-Forming Reactions of Allylic Alcohol Derivatives", **2013**, *Eur. J. Org. Chem.*, 8.
10. "Intramolecular [2+2+2] cycloaddition of bis(propargylphenyl)carbodiimides: synthesis of L-shaped pi-extended compounds with pyrrolo[1,2-*a*][1,8]naphthyridine corner units", **2013**, *Chem. Commun.*, 14.
11. "First total synthesis of (+)-heteroplexisolide E", **2012**, *Tetrahedron Lett.*, 10.
12. "Synthesis of Benzimidazole-Fused Heterocycles by Intramolecular Oxidative C-N Bond Formation Using Hypervalent Iodine Reagents", **2011**, *Synthesis*, 22.
13. "A formal total synthesis of (-)-brevisamide", **2011**, *Tetrahedron Lett.*, 11.
14. "Palladium-Catalyzed Highly Regio- and Stereoselective Synthesis of 4-Alkylidene-4*H*-3,1-benzoxazines from *N*-Acyl-*o*-alkynylanilines", **2011**, *Org. Lett.*, 39.
15. "TBAF-Promoted Elimination of Vicinal Dibromides Having an Adjacent O-Functional Group: Syntheses of 2-Bromoalk-1-enes and Alkynes", **2011**, *Synthesis*, 12.
16. "Novel One-Pot Method for Chemoselective Bromination and Sequential Sonogashira Coupling", **2010**, *Org. Lett.*, 29.
17. "Synthesis of nitrogen heterocycle-fused 1,2,4-benzothiadiazine-1,1-dioxide, quinazolinone, and pyrrolidinone derivatives with a guanidine joint via sequential aza-Wittig reaction/intramolecular NH-addition cyclization/nucleophilic substitution ring closure methodology, using functionalized carbodiimides as key intermediates", **2010**, *Tetrahedron*, 19.

18. "DBU-Promoted Elimination Reactions of Vicinal Dibromoalkanes Mediated by Adjacent *O*-Functional Groups, and Applications to the Synthesis of Biologically Active Natural Products", **2008**, *Synlett*, 14.

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

none

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age)

Hirofumi Toda (41)

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

Assistant professor, IIIS, University of Tsukuba

Academic degree and specialty

Ph.D. (Sci.); Genetics

Effort: 50%

* Percentage of time that the principal investigator devote to working for the center vis-à-vis his/her total working hours.

Research and education history

2016-2019 Research Specialist at HHMI/ University of Pennsylvania, PA, USA
2013-2016 Research Associate at HHMI/University of Pennsylvania, PA, USA
2010-2013 Postdoctoral fellow at Institute of Molecular Pathology, Vienna, AT
2004-2009 D.Sc. Department of Biological Sciences, Graduate School of Life and Environmental Sciences, University of Tsukuba, Ibaraki, Japan
2004-2009 Visiting graduate student at the City of Hope, CA, USA
2002-2004 M.Sc. Department of Biological Sciences, Graduate School of Life and Environmental Sciences, University of Tsukuba, Ibaraki, Japan
2001-2002 Visiting foreign intern at The Rockefeller University, NY, USA
1998-2002 B.Sc. College of Biological Sciences, School of Science, University of Tsukuba, Ibaraki, Japan

Achievements and highlights of past research activities

1. Discovery of a cargo-motor complex machinery in the axonal transport system: He found unc-51/atg1-mediated phosphorylation of an adaptor protein that regulates its assembly to the motor protein.

2. Identification of the sensory neurons that detect female aphrodisiac pheromone: He found *ppk23* positive neurons in the male foreleg that detect female pheromone to elicit courtship behavior.

3. Discovery of a novel sleep-inducing gene, *nemuri*: He found a novel sleep-inducing factor, *nemuri* encoding an anti-microbial peptide induced by infection and involved in infection-

induced sleep, showing that Nemuri links sleep and immunity.

Achievements

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

a) Recipient of international awards

EMBO Long term fellowship

b) Member of a scholarly academy in a major country

N.A.

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

Guest speaker at World Sleep Society 2019 in Vancouver

d) Editor of an international academic journal

N.A.

e) Peer reviewer for an overseas competitive research program (etc.)

N.A.

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

N.A.

(3) Major publications (Titles of major publications, year of publication, journal name, number of citations)

'A sleep-inducing gene, *nemuri*, links sleep and immune function in *Drosophila*', 2019, Science, 28

'The Drosophila female aphrodisiac pheromone activates *ppk23*(+) sensory neurons to elicit male courtship behavior.', 2012, Cell Rep., 103

'UNC-51/ATG1 kinase regulates axonal transport by mediating motor–cargo assembly', 2009, Genes&Dev., 116

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

N.A.

Appendix 3-1 FY 2019 Records of Center Activities

1. Researchers and center staff, satellites, partner institutions

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

- Regarding the number of researchers at the Center, 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. Hirofumi Toda, a sleep research specialist using fruit flies, was recruited from U. Penn as a new PI and started his research group newly furnished with a fly lab at the IIIS in July, 2019. To enhance our administrative supports, we are recruiting Dr. Mayumi Kimura from WPI-IRCN, Tokyo University as a leader of Research Strategy & Management Team from June, 2020. She has a strong background in sleep medicine with 15-year experience at Max Planck Institute in Germany. She is also a potential candidate of Vice Administrative Director of IIIS.

Dr. Yu Hayashi, current IIIS-PI, will move to Kyoto University as a full-professor from April 1st, 2020, yet he will remain with us as a visiting professor of the IIIS and serves as a Satellite PI.

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 overseas, 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	
University of Texas Southwestern Medical Center	Robert Greene	
University of Texas Southwestern Medical Center	Carla Green	
University of Texas Southwestern Medical Center	Qinghua Liu	Quit
University of California, Berkeley	Yang Dan	
Akita University Graduate School of Medicine	Kazuo Mishima	
Ibaraki Prefecture/Ibaraki Prefectural Medical Center of Psychiatry	Takashi Kanbayashi	
Graduate School of Pharmaceutical Sciences, Kyoto University	Hitoshi Okamura	
National Institute of Biological Sciences	Qinghua Liu	

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
RIKEN Brain Science Institute	Shigeyoshi Itohara	
JAXA Space Biomedical Research Office	Satoshi Furukawa	
Gui de Chauliac Hospital	Yves Dauvilliers	

Wenzhou Medical University	Jiang-Fan Chen	
The Jikei University	Megumi Shimoyama	
RIKEN Center for Biosystems Dynamics Research	Genshiro Sunagawa	New
RIKEN Center for Advanced Intelligence Project	Jun Seita	New

2. Holding international research meetings

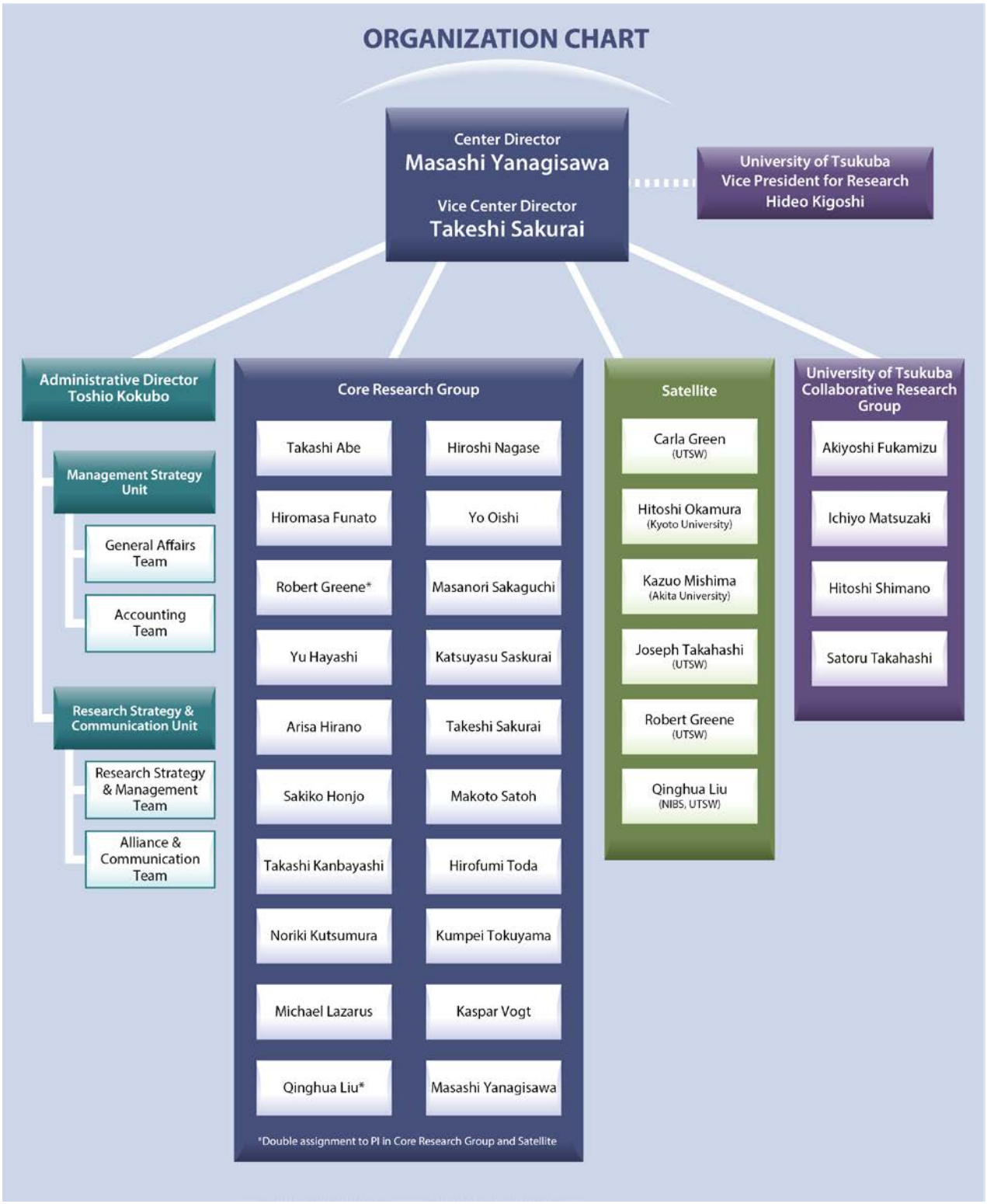
- Indicate the number of international research conferences or symposiums held in FY2019 and give up to three examples of the most representative ones using the table below.

FY 2019: 1 meeting

Major examples (meeting titles and places held)	Number of participants
The Joint Symposium of WPI-IIIS, Ph.D. Program in Humanics, and 36th Takamine Conference, "Fusion of Biomedical and Physical/Informational Sciences in Neurobiology" Date: November 26 Venue: Tokyo Conference Center Shinagawa	From domestic institutions: 207 From overseas institutions: 8

3. Diagram of management system

- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any new changes have been made in the management system from that in the latest "center project" last year, describe them. Especially 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).



4. Campus Map

- Draw a simple map of the campus showing where the main office and principal investigator(s) are located.

5. Securing external research funding*

External research funding secured in FY2019

Total: 807,579,927 yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.
* External research funding includes “KAKENHI,” funding for “commissioned research projects,” “joint research projects,” and for others. (donations, etc.)

Appendix 3-1a FY 2019 Records of Center Activities

Researchers and other center staff

Number of researchers and other center staff

* Fill in the number of researchers and other center staff in the table blow.
* Describe the final goals for achieving these numbers and dates when they will be achieved described in the last "center project."

a) Principal Investigators

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

(number of persons)

	At the beginning of project	At the end of FY 2019	Final goal (March 31, 2022)
Researchers from within the host institution	5	6	8
Researchers invited from overseas	1	11	6
Researchers invited from other Japanese institutions	1	12	10
Total principal investigators	7	29	24

b) Total members

	At the beginning of project		At the end of FY2019		Final goal (March 31, 2022)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	41		77		62	
Overseas researchers	1	2	24	31.2%	21	34
Female researchers	8	20	25	32.5%	22	36
Principal investigators	7		29		24	
Overseas PIs	1	14	8	27.6%	8	33
Female PIs	0	0	4	13.8%	4	17
Other researchers	0		18		15	
Overseas researchers	0	0	1	5.6%	1	7
Female researchers	0	24	4	22.2%	4	27
Postdocs	34		30		23	
Overseas postdocs	0		15	50.0%	12	52
Female postdocs	8		17	56.7%	14	61
Research support staffs	17		17		20	
Graduate students	4		30		68	
Administrative staffs	14		25		19	
Total number of people who form the "core" of the research center	76		149		169	

Appendix 3-2 Project Expenditures

1) Overall project funding

* In the “Total costs” 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 of the "Details" column 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	54	41
	Principal investigators (no. of persons): 15	137	78
	Other researchers (no. of persons): 38	248	171
	Research support staff (no. of persons): 5	37	13
	Administrative staff (no. of persons): 18	71	59
	Subtotal	547	362
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons): 0		
	Cost of dispatching scientists (no. of persons): 0		
	Research startup cost (no. of persons): 27	32	32
	Cost of satellite organizations (no. of satellite organizations): 2	22	22
	Cost of international symposiums (no. of symposiums): 1	5	5
	Rental fees for facilities	70	57
	Cost of consumables	14	14
	Cost of utilities	84	0
	Other costs	43	43
	Subtotal	270	173
Travel	Domestic travel costs	2	2
	Overseas travel costs	1	1
	Travel and accommodations cost for invited scientists (no. of domestic scientists): 0 (no. of overseas scientists): 0		
	Travel cost for scientists on transfer (no. of domestic scientists): 0 (no. of overseas scientists): 1	1	1
	Subtotal	4	4
Equipment	Depreciation of buildings	0	0
	Depreciation of equipment	789	388
	Subtotal	789	388
Research projects (Detail items must be fixed)	Project supported by other government subsidies, etc. *1		
	KAKENHI	265	0
	Commissioned research projects, etc.	270	0
	Joint research projects	72	0
	Ohers (donations, etc.)	29	0
	Subtotal	636	0
Total		2246	927

Costs (Million yens)

WPI grant in FY 2019	556
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
Costs of equipment procured	18
IVC mice cage racks (Number of units: 3)	9
Lab benches (Number of units: 2)	2
Others	7

*1. Management Expenses Grants (including Management Enhancements Promotion Expenses (機能強化経費)), subsidies including 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 KAKENHI or under commissioned research projects or joint research projects, the amounts should be entered in the “Research projects” block.

*1 運営費交付金（機能強化経費を含む）、国立大学改革強化推進補助金等の補助金、間接経費、その他大学独自の取組による学内リソースの配分等による財源
*2 科研費、受託研究費、共同研究費等によって人件費、旅費、設備備品等費を支出している場合も、その額は「研究プロジェクト費」として計上すること

2) Costs of satellites

(Million yens)

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

Appendix 4 FY 2019 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY 2019 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. 2020 and not described in Appendix 1.

Overseas Satellite 1 University of Texas Southwestern Medical Center (Total: 2 paper)

1) (52) Lazarus M, Oishi Y, Bjorness TE, *Greene RW* (2019) Gating and the need for sleep: dissociable effects of adenosine A(1) and A(2A) receptors. *Front Neurosci* **13**. doi:10.3389/fnins.2019.00740

2) (69) Mohawk JA, Cox KH, Sato M, Yoo SH, Yanagisawa M, Olson EN, *Takahashi JS* (2019) Neuronal myocyte-specific enhancer factor 2d (mef2d) is required for normal circadian and sleep behavior in mice. *J Neurosci* **39**(40): 7958-7967. doi:10.1523/JNEUROSCI.0411-19.2019

Overseas Satellite 2 National Institute of Biological Sciences, Beijing (Total: 0 paper)

Overseas Satellite 3 University of California, Berkeley (Total: 0 paper)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2019. 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
FY2019	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
FY2019	0	3	0	0	3
	0	0	0	0	0

Overseas Satellite 2: University of California, Berkeley

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2019	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
FY2019	0	0	0	0	0
	0	0	0	0	0

Overseas Satellite 3: National Institute of Biological Sciences, Beijing

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2019	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
FY2019	4	1	0	0	5
	2	0	0	0	2

Appendix 5　FY 2019 Visit Records of Researchers from Abroad

* If researchers have visited/ stayed at the Center, provide information on them in the below table.

Total: 28

	Name	Age	Affiliation		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)
			Position title, department, organization	Country				
1	Qinghua Liu	48	International Institute for Integrative Sleep Medicine University of Tsukuba National Institute of Biological Sciences, Beijing Tsinghua University	Japan China	Ph.D. Biochemistry Molecular biology	・John J. Trentin Award for Scholastic Excellence Baylor College of Medicine, Houston (1995) ・Alexander Wang Memorial Award for Excellent Biomedical Research Baylor College of Medicine, Houston (2000) ・W. A. “Tex” Moncrief Jr. Scholar in Biomedical Research UT Southwestern Medical Center, Dallas (2004-2008) ・Damon Runyon Scholar Award Damon Runyon Cancer Research Foundation, New York (2005-2007) ・Member of Editorial Board, Journal of Biological Chemistry (2012- Present) ・Member of American Society of Biochemistry & Molecular Biology (2008- Present) ・“百聚” Foreign Talents (2018)	2019 April (4 days) 2019 May (8 days) 2019 July (3 days) 2019 October (5 days) 2019 November (6 days)	Participation in Site Visit Short-term stay for joint research, attendance of PI meetings every month and attendance of international meetings on behalf of IIIS Participation in IIIS symposium
2	Robert W. Greene	69	University of Texas Southwestern Medical Center, Departments of Psychiatry and Neuroscience Peter O’ Donnell Brain Institute University of Tsukuba, International Institute for Integrative Sleep Medicine	U.S.A. Japan	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) ・Awarded NIH T32 Training awards for Sleep and Circadian Rhythms, Director (2018)	2019 April (20 days) 2019 July (5 days) 2019 August (4 days) 2020 February (8 days)	Participation in Site Visit Short-term stay for joint research, attendance of PI meetings every month and attendance of international meetings on behalf of IIIS
3	Kingman Perkins Strohl	71	Department of Physiology & Biophysics, Case Western Reserve University School of Medicine	U.S.A	M.D,	・American Society for Clinical Investigation (1987) ・NIH/NHLBI-Mentored Clinical Scientist Recognition Award (1998) ・Distinguished Achievement Award, American Thoracic Society (2008) ・Faculty Clerkship Teaching Award, Case Western Reserve University School of Medicine (2011) ・Distinguished Speaker and Honoree for Distinguished Foreign Scholar, Chinese Sleep Research Society, Beijing China July, (2014) ・Commendation, Cleveland City Council for Sleep Medicine and Public Service: November (2014) ・Top 10 Clinical Research Achievement Awards honoree (for2014), Clinical Research Forum, Washington DC, April, 2015 (2015) ・Excellence in Education Award, American Academy of Sleep Medicine, Boston, Massachussett (2018)	2019 April (2 days)	Lecture at IIIS seminar Having scientific meeting with PIs
4	Marry J. Morrell		Sleep and Respiratory Physiology, Imperial College London	UK	Ph.D. Science	・Board of Directors & Chair, Respiratory, Sleep and Neurobiology Assembly (RNS) (elected) American Thoracic Society (2007–2009) ・Chair, Scientific Program Committee European Sleep Research Society (2008) ・Committee Member, Education Committee (invited); Nominating Committee (2009–2011) ・Chair of Policy Committee; Executive Committee & Board of Trustees The Physiological Society (2012–2016) ・President British Sleep Society (2015–2017)	2019 April (2 days)	Lecture at IIIS seminar Having scientific meeting with PIs
5	Christian Tietje	52	Director, Professor Institute for Economic Law/ Director Transnational Economic Law Research Center (TELC)/ Professor Martin Luther University Halle-Wittenberg	Germany	Ph.D. Political Science	・Studies in Law and Political Science at the Freie Universität Berlin and the Université Paris I – Panthéon-Sorbonne (1999–2005) ・New York University School of Law, LL.M. in International Legal Studie (2006-2007) ・Litigation Associate, Cravath, Swaine & Moore LLP, New York & London (2007-2010) ・Expert in German Law, Israel Democracy Institute (2013) ・Senior Research Lecturer, Chair for Public Law, European Law and International Economic Law, Martin-Luther-Universität Halle-Wittenberg (2014)	2019 May (1 day)	Visit to IIIS research facilities and meeting with Director
6	Henning Rosenau	55	Professor of Criminal Law, Criminal Procedure Law and Medical Law Martin Luther University Halle-Wittenberg	Germany	Ph.D. Physics	・Member of the Standing Commission on Organ Transplantation of the German Medical Associationsince (2006) ・ Vice-Chairman of the Genetic Diagnostics Commission (2009-2016) ・member of the executive board of the working group "Doctors and Lawyers" of the Working Group of Scientific Medical Societies (2012-) ・Vice-President for International And Research at the University of Augsburg (2013-2015) ・Chairman of the Genetic Diagnostics Commission (2016-)	2019 May (1 day)	Visit to IIIS research facilities and meeting with Director
7	Gesine Foljanty-Jost	67	Professor, Martin Luther University Halle-Wittenberg	Germany	Ph.D. Political Science	・Received the Order of the Rising Sun, Golden Rays on a Ribbon from the Japanese government (2014) ・Honored the DFG with the Eugen and Ilse Seibold Prize (2015) ・Awarded the Federal Cross of Merit on ribbon by the Federal Republic of Germany (2016)	2019 May (1 day)	Visit to IIIS research facilities and meeting with Director
8	Reinhard Krause-Rehberg		Professor Faculty of Science 2, Institute for Physics Martin Luther University Halle-Wittenberg	Germany	Ph.D. Physics	・Studied physics at the Martin Luther University Halle-Wittenberg (1976-1981) ・Head of the positron laboratory (1986-) ・Gustav Hertz Medal of the Physical Society of the GDR for research groups for the "Contributions to the investigation of crystal defects in metals and semiconductors with positrons" (1987) ・Research stay at the "Laboratory of Physics" at the Helsinki University of Technology (1990)	2019 May (1 day)	Visit to IIIS research facilities and meeting with Director
9	Ying Ma		Department of Life Sciences, Imperial College London	UK	Ph.D. Neuroscience	・Visiting Researcher, Imperial College London (2014-2015) ・Research Assistant, Imperial College London (2018-2020)	2019 May (1 day)	Participation in seminar as a speaker
10	Azamat Kibekbaev		Kyrgyz Governmental University of Science Technology and Architect	Kyrgyz Republic	Ph.D. Industrial Engineering	・TUSKON Trade Organization, Translator, Istanbul (2007) ・Fifth World Water Form 2009, Minister Assistant, Istanbul (2008) ・SGEM Company, Mega Structure Department, Kyrgyzstan (2010)	2019 June (1 day)	Visit to IIIS research facilities and meeting with Director

11	Maithe Arruda Carvalho		University of Toronto Scarborough Department of Psychology	Canada	Ph.D. Neuroscience	・Young investigation Award (Brazilian Society of Clinical Investigation): First Prize Federal Society of Experimental Biology Annual Meeting (2004) ・Bioresearch Award for young Investigation, Bioresearch and Brazilian Society of Biochemistry and Molecular Biology (2004) ・Honor Certificate for Poster Presentation, Federal Society of Experimental Biology Annual Meeting, Brasil (2004-2006) ・University of Toronto Neuroscience Program Travel Award for the Meeting of the Society of Neuroscience 2009 in Chicago (2009) ・Keystone Symposia Travel Scholarship for the Keystone Symposia on Adult Neurogenesis in Taos, New Mexico (2010) ・Hospital for Sick Children Trainee Start-up Fund for travelling to Dr. Shaoyu Ge's lab in Stony Brook, NY (2011) ・American College of Neuropsychopharmacology (ACNP) Travel Award (2017) ・Society of Biological Psychiatry Travel Award (2018) ・Human Frontier Science Program (HFSP) Career Development Award (2018) ・SickKids Foundation and Canadian Institutes of Health Research [CIHR - Institute of Human Development, Child and Youth Health (IHDCYH)] New Investigator Research Grant (2019)	2019 July (1 day)	Lecture at IIIS seminar Having scientific meeting with PIs
12	Paul Frankland		Hospital for Sick Children Research Institute / University of Toronto	Canada	Ph.D. Neuroscience	・UCLA Chancellors Award for Postdoctoral Research (2002) ・Molecular and Cellular Cognition Society Young Investigator prize (2003) ・Canada Research Chair in Cognitive Neurobiology (Tier 2) (2004-2013) ・The Eppendorf & Science Prize for Neurobiology, Finalist (2005) ・EJLB foundation scholar (2006-2009) ・Visiting scientist at Tokyo University of Agriculture (2006-) ・Canada Research Chair in Cognitive Neurobiology (Tier 1) (2016-2023) ・Senior Fellow, Canadian Institute for Advanced Research (2016-) ・Fellow, Royal Society of Canada (Life Sciences division) (2018)	2019 July (2 days)	Lecture at IIIS seminar Having scientific meeting with PIs
13	Franziska Bender		Perception and Memory Laboratory, Institut Pasteur	France	Ph.D. Neuroscience	・Young investigator orals, The 11th Göttingen Meeting of the GNS (2015) ・Young investigator orals, The 12th Göttingen Meeting of the GNS (2017) ・Travel grant awarded by the FMP graduate school to attend SfN Meeting (2017) ・Travel grant award to attend FENS Regional Meeting (2017) ・The Human Frontier Science Program Long-Term Fellow (2019)	2019 July (1 day)	Visit to IIIS research facilities and meeting with Director
14	Matilde Galli		Hubrecht Institute	Netherland	Ph.D. Biology	・Recipient of a NWO Rubicon Fellowship (2012) ・Recipient of a HFSP Postdoctoral Fellowship (2012) ・Recipient of a Dutch Cancer Society (KWF) Fellowship for Basic Research (2014) ・Recipient of a NWO Veni career grant (2017) ・Recipient of an HFSP Career Development Award (2017)	2019 July (1 day)	Visit to IIIS research facilities and meeting with Director
15	Xin Bian		Boyer Center for Molecular Medicine, Yale University School of Medicine	U.S.A.	Ph.D. Cell and Molecular Biology	・The Human Frontier Science Program Long-Term Fellow (2016)	2019 July (1 day)	Visit to IIIS research facilities and meeting with Director
16	Ilaria Panzeri		Center for Epigenetic, Van Andel Research Institute	U.S.A.	Ph.D. Translational and Molecular Medicine	・"Enrico Legler" Award (2011) ・Travel grant poster Italian Society of Biophysics and Molecular Biology (2015) ・The European Molecular Biology Organization Travel Grant (2015) ・Epigen Travel grant (2017) ・The Human Frontier Science Program Postdoctoral Fellowships (2018)	2019 July (1 day)	Visit to IIIS research facilities and meeting with Director
17	Shady Saad		Chemical and Systems Biology Department, Stanford University	U.S.A.	Ph.D. Biology	・Long-Term Fellowship, Human Frontier Science program (HFSP) ・Early postdoc mobility Fellowship, Swiss National Science Foundation (SNF)	2019 July (1 day)	Visit to IIIS research facilities and meeting with Director
18	Emily Standen		Dept. of Biology, University of Ottawa	Canada	Ph.D. Biology	・Honours double major: Marine Biology & Oceanography (1995) ・The Human Frontier Science Program Grant (2017)	2019 July (1 day)	Visit to IIIS research facilities and meeting with Director
19	Alex Thornton		Centre for Ecology and Conservation, University of Exeter	UK	Ph.D. Zoology	・Cambridge Philosophical Society Studentship (2006) ・British Ecological Society Research Grant (2010) ・David Phillips Research Fellowship: The evolution of corvid intelligence (2010) ・Australian Research Council (2014) ・Biotechnology and Biological Sciences Research Council (2014) ・The Economic and Social Research Council (2015) ・The Human Frontier Science Program Grant (2017)	2019 July (1 day)	Visit to IIIS research facilities and meeting with Director
20	Elvin Wagenblast		Princess Margaret Cancer Centre, University Health Network/ University of Toronto	Canada	Ph.D. Biological Sciences	・Heidelberg-Cornell Exchange Fellowship (2007) ・Fulbright Fellowship (2007) ・Starr Centennial Scholar (2008) ・Boehringer Ingelheim Fonds Ph.D. Fellowship (2009) ・Human Frontier Science Program Long-Term Fellowship (2016) ・Banting Postdoctoral Fellowship (2018)	2019 July (1 day)	Visit to IIIS research facilities and meeting with Director

21	Kong Y. Chen		Metabolic Clinical Research Unit, NIH Clinical Center / The National Institute of Diabetes and Digestive and Kidney Diseases	U.S.A.	Ph.D. Biomedical Engineering	・Young Investigator of the Year, Clinical Nutrition Research Unit Vanderbilt University (1999 and 2000) ・External Advisor, Vanderbilt University T32 “Research Training in Childhood Obesity” (2011-2012) ・National Children’s Hospital Bionutrition Program Board of Advisors (2009-2010) ・Vanderbilt University School of Engineering Committee of Visitors (Board of Advisors to the Dean) (2008-2012) ・NIDDK Office of Minority Health Research Coordination Mentoring Leadership Award (2010) ・NIDDK Director’s Award (2012) ・NIH Clinical Center Director’s Award (2014) ・Tennessee Technological University School of Engineering Board of Advisers (2017-)	2019 September (1 day)	Lecture at IIIS seminar Having scientific meeting with PIs
22	David Prober		Division of Biology and Biological Engineering, California Institute of Technology	U.S.A.	Ph.D. Molecular/Cellular Biology	・Governor-General's Medal (1991) ・Canada Scholarship (1991) ・Alumni Association Entrance Scholarship (1991) ・Isbister Scholarship in Science (1991) ・Benjamin Cohen Scholarship (1991) ・NSERC University Undergraduate Research Award (1992) ・Edna Hollier Scholarship (1993) ・Princess of Wales' Canada Scholarship in Biological Sciences (1993) ・Mindel and Tom Olenick Medal and Prize (1995) ・National Science Foundation Predoctoral Fellowship (1997) ・Howard Hughes Medical Institute Predoctoral Fellowship Honorable Mention (1997) ・Harold M. Weintraub Graduate Student Award (2001) ・Helen Hay Whitney Foundation Postdoctoral Fellowship (2003) ・Sleep Research Society Young Investigator Award (2007) ・NIH Pathway to Independence Award (K99/R00) (2007) ・Edward Mallinckrodt Jr. Foundation Award (2010) ・Esther and Joseph Klingenstein Fund Fellowship (2010) ・Rita Allen Foundation Scholar (Milton E. Cassel Scholar) (2010) ・NARSAD Young Investigator Award (2010)	2019 October (2 days)	Lecture at IIIS seminar Having scientific meeting with PIs
23	Erick D. Herzog		Department of Biology, Washington University	U.S.A.	Ph.D. Neuroscience	・Graduation cum laude, with distinction, Duke University (1987) ・CALS Scholarship for first place in scientific writing competition, U of Wisconsin (1988) ・Outstanding Teaching Assistant Award, Syracuse University (1993) NIH Shannon Award (1998 – 2000) ・Visiting Fellow, Japanese Society for the Promotion of Science (2007) ・Outstanding Faculty Mentor Award, Washington U. Graduate Student Senate (2008) ・Special Recognition Mentor Award, Washington U. Graduate Student Senate (2010) ・Outstanding Faculty Mentor Award, Washington U. Postdoctoral Society (2010) ・Honorable Mention for Faculty Mentor of the Year, WU Office of Undergrad Research (2011) ・Visiting Scholar, Bernstein Center for Computational Neuroscience, Berlin, Germany (2012) ・Excellence in Advising and Mentoring Award, WU Arts and Sciences Council (2014) ・Bauer Foundation Distinguished Lecturer, Brandeis University (2015) ・James E. McLeod Faculty Teaching Award, ArtSci Council, WU (2015) ・Mead Johnson Lecturer, Perinatal Research Society (2017) ・Konopka Symposium Lecturer, Society for Research on Biological Rhythms (2018) ・The Award for Education in Neuroscience, Society for Neuroscience (2018)	2019 October (1 day)	Lecture at IIIS seminar Having scientific meeting with PIs
24	Mathias Treier		Max-Delbrück Center for Molecular Medicine in the Helmholtz Association / Charité University Medicine Berlin	Germany	Ph.D. Molecular Biology	・EMBL Ph.D. fellowship (1991) ・Boehringer Ingelheim Postdotoral fellowship (1995) ・California Breast Cancer fellowship (1997) ・Nuffield Professorship of Obstetrics and Gynaecology, University of Oxford, UK (2010)	2019 October (3 days)	Lecture at IIIS seminar Having scientific meeting with PIs
25	Henrik Bringmann	41	Animal Physiology / Neurophysiology (W3), University of Marburg, Germany	Germany	Ph.D. Biology	・Pre-Diploma examination results: 1.0 (best-possible result), University of Göttingen, Germany (2001) ・Scholarship of the German National Merit Foundation (Studienstiftung des deutschen Volkes) (2001-2003) ・Diploma marks 1.0, received “with distinction” (best-possible result), University of Heidelberg, Germany (2003) ・Predoctoral Fellowship/ Boehringer Ingelheim Fonds / Germany (2004-2007) ・PhD received with “summa cum laude” (“with highest distinction”, best-possible result) received from The Technical University Dresden / Germany (2007) ・Otto Hahn Medal of the Max Planck Society (2008) ・European Research Council Starting Grant “SLEEPCONTROL” (2015) ・Three evaluations of the Max Planck Research Group “Sleep and Waking” as “excellent“ by the Scientific Advisory Board of the Max Planck Institute of Biophysical Chemistry Göttingen, Germany (2009-2018)	2019 November (3 days)	Participation in symposium as a speaker Lecture at IIIS seminar Having scientific meeting with PIs
26	Antoine Bocquet		Managing Director, Nature Japan K.K/ Springer	Japan, South East Asia and Oceania	Ph.D. Physics	・Director, Asia-Pacific, Nature Publishing Group (2011-2014) ・MSS Director, Asia excluding Greater China (2014-2015) ・Executive Vice President, Nature Japan K.K.(2001-2012) ・CEO and Representative Director, Nature Japan K.K.(2012-)	2020 February (1 day)	Visit to IIIS research facilities and meeting with Director Lecture at Publishing seminar
27	Jacco Flipsen		Vice President, Journals, Mathematics, Physical & Applied Sciences, Springer Nature	Netherland	Ph.D. Biochemistry	・Chairman and member of Works Council (2001-2005) ・Vice President Publishing, Life Sciences (2014-2018) ・Director Springer Nature B.V., Dordrecht, The Netherlands (2016-) ・Vice President, Medicine and Life Sciences Journals (2019-)	2020 February (1 day)	Visit to IIIS research facilities and meeting with Director Lecture at Publishing seminar
28	Harry Blom		Vice President, Journals, Development, Policy & Strategy, Springer Nature	U.S.A.	Ph.D. Astrophysics	・Editorial Director for Physics and Astronomy (2006-2010) ・Editorial Director for Astronomy and Brazilian Market Development (2010-2013) ・Vice President Publishing Development (2013-2015) ・Vice President Mathematics, Computer Science, and Publishing Development (2015-2018) ・Vice President Journals, Development, Policy & Strategy (2019-)	2020 February (1 day)	Visit to IIIS research facilities and meeting with Director Lecture at Publishing seminar

Appendix 6 FY2019 State of Outreach Activities

* Fill in the numbers of activities and times held during FY2019 by each activity.
* Describe the outreach activities in the "6. Others" of Progress Report, including those stated below that warrant special mention.

Activities	FY2019 (number of activities, times held)
PR brochure, pamphlet	2
Lectures, seminars for general public	42
Teaching, experiments, training for elementary, secondary and high school students	20 (2 was canceled due to concern of COVID-19)
Science café	0
Open houses	1
Participating, exhibiting in events	6
Press releases	17
Publications of the popular science books	1
Others (Internet Broadcasting)	2

*If there are any rows on activities the center didn't implement, delete that (those) row(s). If you have any activities other than the items stated above, fill in the space between parentheses after "Others" on the bottom with the name of those activities and state the numbers of activities and times held in the space on the right. A row of "Others" can be added, if needed.

Outreach Activities and Their Results

List the Center's outreach activities carried out in FY 2019 that have contributed to enhancing the brand or recognition of your Center and/or the brand of the overall WPI program, if any, and describe its concrete contents and effect in narrative style. (Where possible, indicate the results in concrete numbers.)

Examples:
- As a result of using a new OO press-release method, a OO% increase in media coverage was obtained over the previous year.
- By holding seminars for the public that include people from industry, requests for joint research were received from companies.
- We changed our public relations media. As a resulting of using OO to disseminate information, a OO% increase in inquiries from researchers was obtained over the previous year.
- As a result of vigorously carrying out OO outreach activity, ¥OO in external funding was acquired.

- Live broadcast at Nico Nico Cho-Kaigi on April 27 and 28 increased the number of visitors to the official IIIS website by 47.4% compared to the previous year.

- Our active endeavor in accepting school group visitors so successful that one student enrolled University of Tsukuba and started sleep research at IIIS. Several students who visited IIIS are also considering University of Tsukuba in 2020.

- We opened a booth at Kagaku-Zammai in Aichi 2019 and had talk shows to promote our research activities, which attracted more than 300 audiences in total. We were also very well received with a similar booth opened at "WPI Science Symposium," targeted mainly for adults this time.

- Articles published on "Newton" and "Newton Extra Issue" featuring our research activities received a number of positive responses from a wide range of people who are interested in sleep science. The articles are also very well-used as a side reader for school visitors.

Appendix 7 FY 2019 List of Project's Media Coverage

* List and describe media coverage (e.g., articles published, programs aired) in FY2019.

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
1	2019/4/4	NHK "NHK News" (Television)	Nature's 150th anniversary symposium event report A Japanese perspective on the SDGs (Yanagisawa)
2	2019/4/23	The Asahi Shimbun (Newspper)	Young man overcomes sleep disorder to enter medical school (Yanagisawa)
3	2019/4/25	Nikkei Science (Magazine)	Feature article: What is sleep? ~scientific approaches to the neural sebstance of sleepiness (Yanagisawa)
4	2019/4/29	Tokyo Shimbun, Chunichi Shimbun (Newspaper)	The great function of your brain ~What is happening your brain during sleep?~ (Hayashi)
5	2019/5/6	Tokyo Shimbun, Chunichi Shimbun (Newspaper)	Sleep and evolution ~Both humans and jellyfish sleep~ (Hayashi)
6	2019/6/1	Nature Digest (Magazine/Web)	Nature and me (Yanagisawa)
7	2019/6/18	NHK Radio Radio Shinya-bin (Radio)	What is the substance of sleepiness? (Yanagisawa)
8	2019/6/26	Newton (Magazine)	Feature article: The new golden rules for sound sleep from cutting edge science for sleep (Yanagisawa)
9	2019/6/28 2019/7/1	Nature Asia, Nature Digest, Nature Research Web (Magazine/Web)	Nature's 150th anniversary symposium event report A Japanese perspective on the SDGs (Yanagisawa)
10	2019/8/30	The Asahi Shimbun (Newspper)	Orthostatic dysregulation and its treatment (Kanbayashi)
11	2019/9/4	anan (Magazine)	Love Sleep! ~Mechanisms of sleep and basics of good sleep~ (T. Sakurai)
12	2019/9/23	The Early Edition with Stephen Quinn (Radio) *Canada	Solving the mysteries of sleep (Yanagisawa)

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
13	2019/10/5	Newton, Extra Issue (Mook)	The golden rules for sound sleep (Yanagisawa)
14	2019/10/23 2019/11/21	Nikkei Sangyo Shimbun, Nikkan Kogyo Shimbun (Newspaper)	Reseachers at Toho University and University of Tsukuba reveal that orexin neurons are involved in the regulation of energy metabolism and body weight (Press release: Kakizaki, Funato, Yanagisawa)
15	2019/10/29	NHK "NHK News" (Television) The Asahi Shimbun, Nikkei Shimbun, The Yomiuri Shimbun, The Mainich Shimbun, and more (Newspaper)	Persons of curtural merit to be awarded to Professor Masashi Yanagisawa (Yanagisawa)
16	2019/11/2 2019/11/5	AERA/ AERA. jp (Magazine/Web)	The best way to spend 24 hours: Advice from brain science (T. Sakurai)
17	2019/11/16	BRIC (Web) *Korea	Korean people who is shining abroad (Seol)
18	2019/11/7 2019/11/14	Ibakira TV (Television) The Yomiuri Shimbun, The Ibaraki Shimbun, and more (Newspaper)	Ibaraki prefecture honor award to be awarded to Professor Masashi Yanagisawa (Yanagisawa)
19	2019/11/29	BS Nittere "Shinso News" (Television)	What can you do now for sound sleep? One of the biggest social problem in Japan: Sleep deprivation (T. Sakurai and Mishima)
20	2019/12/1	Gehirn & Geist (Magazine) *Germany	Dich durch Schlafmangel (Lazarus)
21	2019/12/13	The Yomiuri Shimbun (Newspaper)	yomi Dr. : What is the ideak sleep for Japanese? ~To secure enough sleep and prevent lifestyle-related diseases~ (T. Sakurai and Mishima)
22	2020/2/8	The Asahi Shimbun (Newspper)	Nono-cyan's DO Science: Why do we dream during sleep? (Hayashi)
23	2020/3/26	Tarzan (Magazine)	How to Achieve a Comfortable Sleeping Environment (T. Sakurai)