World Premier International Research Center Initiative (WPI)
Executive Summary (For Extension Application Screening)

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

Instruction:
Based on the Center's Progress Report and Progress Plan, prepare this summary within 6 pages.

A. Progress Report of the WPI Center

I. Summary

International Institute for Integrative Sleep Medicine (IIIS) has been established *de novo* in University of Tsukuba as the WPI center for sleep science, aiming to solve the medical and social issues related to sleep by elucidating mechanism of sleep/wake regulation and molecular pathogenesis of sleep disorders, and developing sleep disorder treatments. Despite the fact that most of its PIs were recruited from institutions outside University of Tsukuba at/after its inauguration, IIIS has already achieved four objectives of the WPI program:

Advance cutting-edge research: Numerous ground-breaking results have been achieved. The research achievements of IIIS are highly recognized in and outside Japan, and IIIS researchers have received many awards. Besides many papers published in scientific journals, 18 patent applications have been filed so far, aiming at practical applications of research results.

Establish international research environment: More than 30% of researchers from overseas actively participated in the research activities at IIIS. We host International Symposium every year, and to the 7th WPI-IIIS Symposium in FY 2018, 4 outstanding foreign researchers were invited. On the other hand, WPI-IIIS Seminars were held 17 times in FY 2018 and 8 speakers from overseas gave lectures and the ratio of foreign speakers was 47% of the total seminar speakers.

Reform research organization: The basic concepts of the organization and the operation of IIIS involve creating a new style of research center by learning from the merits and virtues in the organization of "departments" in major US universities. We continue the efforts of system reforms in cooperation with University of Tsukuba. In the university, IIIS is positioned as a pioneering model of the forefront research organization the mid-term plan targets.

Create interdisciplinary domains: We conduct wide-ranging sleep research, covering a scope from a) basic biology such as neuroscience, molecular genetics and molecular cell biology to b) pharmaceutical science, and further to c) experimental medicine. We create the new interdisciplinary research domain, "sleep science" by fusing 3 research fields.

II. Items

1. Overall Image of 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. 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. Furthermore, the deficiencies in healthy sleep, which are linked to decrease in working efficiency and increase in accidents due to excessive sleepiness, causes significant social losses as well.

To solve the medical and social issues related to sleep, we set out our major research objectives as follows.

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

To achieve these objectives, we have to conduct wide-ranging sleep research, covering a scope from a) basic biology such as neuroscience, molecular genetics and molecular cell biology to b) pharmaceutical science, and further to c) experimental medicine. We thus aim to create the new interdisciplinary research domain, "sleep science" by fusing 3 research fields.

The basic concepts of the organization and the operation of IIIS involves creating a new style of research center by learning from the merits and virtues in the organization of

"departments" in major US universities. In addition to the strong leadership of the "Department Head," other characteristics including the flat organization, the appointment of PIs regardless of their age and career stage, and flexible/dynamic allocation of the floor space and other resources to labs, have been implemented.

The PI meeting chaired by the Center Director is held every month and serves as the decision-making body in IIIS. There are 8 Labs operated by 13 PIs (5 Co-PIs) in the basic biology. One PI presides a pharmaceutical science Lab with 3 assistant professors, and 3 PIs run 3 Labs in experimental medicine. IIIS (core team) is thus comprised of 12 Labs with 16 PIs (of whom 14 were newly recruited from institutions outside the University of Tsukuba at/after the inauguration of IIIS) and 14 non-PI faculties, 26 researchers, and 61 graduate/undergraduate students. IIIS attracts many students for their dissertation studies and the number of students has been constantly increasing.

The construction of the IIIS Building (6-stories with 8,000 m^2 of floor space) was completed in June 2015. It is located at the north corner of the Hospital Area. The IIIS Building serves as a globally unrivaled venue for conducting interdisciplinary sleep research under one roof, covering 3 research fields of a) basic biology, b) pharmaceutical science and c) experimental medicine. It accommodates 2,600 m^2 of the vivarium exclusive to IIIS on the 5th and 6th floors, and the breeding area on the 6th floor accepts up to 6,000 individually ventilated cages, and there are 7 sleep recording labs and 6 behavior labs in the experimental area on 5th floor, cementing its role as a leading global research resource.

Great efforts to raise research funds were made, and it increased rapidly as ¥282 M in FY 2015, ¥611 M in FY 2016, and ¥667 M in FY 2017. In FY 2018, it reached ¥770 M due to young PI's efforts. The average amount of external funds/person in IIIS was ¥13,500,000, which is twice as large as the average in University of Tsukuba (¥6,120,000 in FY 2017). Since terms of many grants are multiple-years, we have already secured funding of ¥693 M in FY 2019, ¥505 M in FY 2020 and ¥291 M in FY 2021. We continue our efforts to acquire external funding every year to exceed the level of FY 2018.

2. Advancing Research of the Highest Global Level

The three objectives described above are actually the issues of a global level that the Center has challenged, and we provide 15 representative research results to achieve them as follows;

[1] Opening the black box of sleep homeostasis through large-scale forward genetics and phosphoproteomics
[2] The functions of REM sleep revealed from chemogenetic approaches
[3] Deciphering neuronal circuits linking the limbic system, hypothalamus, and brain stem
[4] Experimental dissociation of sleep homeostasis and emotionally/motivationally induced wakefulness
[5] The brain mechanism underlying the desire to sleep in boring situations
[6] Elucidation of the functions of thalamic matrix cells in regulation of cortical activity and arousal
[7] Understanding the biological clock regulating sleep/wake rhythms at cellular and molecular levels
[8] Applying the functional connections between sleep and memory for future therapy
[9] Orexin to locus coeruleus pathway gates fear-related behavior.
[10] A forward genetics screen to uncover the molecular basis of innate fear in mice
[11] Essential yet distinct roles of adenosine A_1 and A_{2A} receptors in sleep gating and function
[12] Clarification of a mystery to scratch skin on feeling itch: Role of spinal dynorphin
[13] Detailed description of energy metabolism during human sleep
[14] The mechanistic therapy of narcolepsy: proof-of-concept
[15] The neuropeptide orexin as a potential anti-inflammatory therapeutic for septic shock

The development of the facilities has been continuously moving forward along with our progress plan. Especially, expansion of the experimental medicine in IIIS had been a pending issue, and we thus newly established a facility for human sleep research, Human Sleep Lab in Innovation Medical Research Institute located in Kasuga Campus, the university as of March 31, 2019.

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.

The research achievements of IIIS are highly recognized in and outside Japan, and IIIS researchers have received many awards. Yanagisawa, for example, has received not only prestigious academic awards, including the Keio Medical Science Prize, but also awards well

known to general public such as Medal with Purple Ribbon and the Asahi Prize, commended for his contribution to the development of culture and society through the sleep research.

Aiming at applications of research results, we have filed 18 patent applications so far. The applications are all commensurate with the research objectives of IIIS, which involves elucidating the sleep-awake regulation mechanisms and the pathogenesis of sleep disorders and developing new treatment methods.

The joint research projects between IIIS and the companies also aim at 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 on sleep-aiding products in collaboration with companies/research institutions.

In order to enhance the visibility of IIIS, we have held lots of outreach events. One of the most outstanding events in the past seven years was the 6th WPI Science Symposium which we organized as a host institute in 2017.

As events to introduce our studies and facility to general public, we broadcasted two Nico Nico Live programs. In the programs, lots of researchers including Yanagisawa, T. Sakurai, other PIs and students at IIIS introduced cutting-edge sleep science and their own studies, interacting with viewers through real-time comments.

3. Generating Fused Disciplines

To achieve these the three objectives of IIIS, 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. It is the new interdisciplinary research domain, “sleep science,” we aim to create by fusing 3 research fields.

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 IIIS-wide meetings such as the Work in Progress (WIP) meeting, the Dojo journal club, and B&B.

As a result, the number of articles by collaborative research has drastically increased since FY 2015. The Nature papers published by Funato et al. in 2016 and 2018 are good examples of the successful internal collaborations involving 4 IIIS labs, in addition to multiple outside collaborators.

As described in Appendix 1-2, in the fused research fields, there are 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) morphine sedative effects, iv) PTSD and v) anxiety disorder, and vi) addiction to smoking, alcohol and psychotropic drugs.

4. Realizing an International Research Environment

The overseas PIs have actively participated in the research activities at IIIS. While Liu and Greene have contributed to IIIS through their research activities in University of Texas Southwestern Medical Center (UTSW) as Satellite PIs, they have also established their own labs as PIs in the core group of IIIS since FY 2013 and engaged in lively research activity. In FY 2018 Liu was appointed to the Investigator of National Institute of Biological Science, Beijing (NIBS) besides UTSW and IIIS, and the Research Collaboration Agreement for the cross-appointment was executed among 3 institutions.

IIIS hosts International Symposium every year since the establishment in 2012. About 200 of researchers and students participate each time, and enjoy lectures by prominent sleep researchers from Japan and abroad and active scientific discussions. To 7th WPI-IIIS Symposium held on December 20, 2018 at Tokyo Conference Center, 4 outstanding foreign researchers were invited from abroad in order to introduce the latest achievements in sleep research and relevant fields. Many invited speakers disclosed unpublished data of their studies, which inspired new ideas and expanded collaboration opportunities.

We hosted 17 WPI-IIIS Seminars in FY 2018, where we invited domestic and foreign researchers in sleep/neuroscience fields almost every other week; 8 speakers from overseas gave us lectures and the ratio of foreign researchers was 47% of the total seminar speakers in FY 2018. Every speaker is asked to spend one whole day to meet individually with all PIs who are in town, so that the seminar day provides PIs opportunities of exchanging research ideas and expanding human networks. Another trend especially worth mentioning is that the number of foreign researchers visiting IIIS has increased significantly. As you can see in

Appendix 4-2, 24 excellent researchers visited IIIS, excluding PIs and the speakers of IIIS Symposia and IIIS Seminars.

Concerning employment of young researchers, in addition to posting job advertisements, we have employed some brilliant researchers through the continued efforts in international recruitment through networks of PIs. We have regularly invited speakers from abroad for the IIIS Seminar series and made use of these opportunities to look for candidates of Junior PIs and postdoctoral researchers. In FY 2018, six foreign researchers (1 Chinese, 1 French, 1 Spanish, 1 Indian, 1 Nepalese, and 1 Korean) joined us including 4 through open international solicitations. Most of them stayed at IIIS to obtain skills and knowledge of sleep research, to advance their career paths.

5. Making Organizational Reforms

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

We continued the efforts of system reforms in cooperation with University of Tsukuba as follows.

1. Introduction of a system to evaluate research results and ability-linked salary system
2. Authority over personnel matters and simplification of the appointment system
3. Joint appointment system
4. Tsukuba Short-term Study Program (TSSP)
5. Establishment of the spin-out of IIIS, S’UIMIN Inc. as a IIIS TLO

During the third mid-term plan of University of Tsukuba starting from FY 2016, the university aims to develop a globally unrivaled frontier research of 2 objectives, i.e., research for the quest for truth and research for innovation contributing to society, in wide-ranging disciplines and research fields. To realize these objectives, the university is making a plan of reorganization/restructuring/merger of all research centers and will implement it during the period of the 3rd mid-term plan. IIIS is positioned as a pioneering model of the forefront research organization the mid-term plan targets, attesting the “ripple effect” of IIIS management.

6. Others

IIIS put forth multiple and unconventional outreach activities. We conducted a crowdfunding project in FY 2018 and successfully raise fund of ¥3,566,000. In addition to public relations activities, the Alliance & Communication team organized the internal events to encourage open communication and collaborations among labs.

R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI) supported by Toyota Motor Corporation has moved into the south side on 4th floor of IIIS Building. We are planning a long-term collaboration with them and, as the first step, we are developing the Mobile Sleep Lab based on a fuel cell bus lent by Toyota at no charge, taking advantage of its characteristics; the fuel cell bus can supply bulk power for air conditioning and sleep measurement without noise and vibration, and access easily to subjects at living/working environment.

To avoid research misconduct, we have launched educational campaigns for research ethics since FY 2015. We have held total five seminars in the series of Research Ethics Seminars. In addition, we introduced the official laboratory notebook of IIIS to formalize and let everyone use a common hard-covered laboratory notebook for better data management and prevention of research misconduct.

World Premier International Research Center Initiative (WPI)
Progress Report of the WPI Center
(For Extension Application Screening)

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

Common Instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2019) situation of your WPI center.
* As a rule, keep the length of your report within the specified number of pages. (The attached forms are not included to this page count.)
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

1. Overall Image of IIIS (write within 2 pages including this page)

Describe the Center's current identity and overall image.
- List the Principal Investigators in Appendix 2, and enter the number of center personnel in Appendix 3-1, 3-2, diagram the center's management system in Appendix 3-3, draw a campus map in Appendix 3-4, and enter project funding in Appendix 3-5, 3-6.

1-1. Background

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 ¥15.4 T/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.

1-2. Research Objectives and New Interdisciplinary Research Domain

To solve the issues, we set out our major research objectives as follows.

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

To achieve these objectives, we have to conduct wide-ranging sleep research, covering a scope from a) basic biology such as neuroscience, molecular genetics and molecular cell biology to b) pharmaceutical science, and further to c) experimental medicine. We thus aim to create the new interdisciplinary research domain, "sleep science" by fusing 3 research fields.

Since these 3 objectives should be achieved in sequence from 1. to 3., and the first one is the most challenging, we put the biggest resources to the basic biology, especially neuroscience. Our studies of neuroscience are making very rapid progress thanks to the development of novel methods such as optogenetics. Quite a few types of neurons in various brain regions and nuclei have been identified to play important roles in the sleep/wake regulation. By tracing their projection and studying upstream neurons, important neural circuits are being elucidated.

Forward genetics is the characteristic approach of our studies to elucidate the fundamental mechanisms of sleep/wake regulation, since there are no reliable hypotheses to perform reverse genetics. It is indeed evident that this method has given us innovative clues to elucidate the mechanisms, i.e., identification of genes regulating sleep/wakefulness.

Drug discovery to develop novel treatments for sleep disorders such as narcolepsy is another characteristics of IIIS. Especially in US, many drug candidate compounds developed by academia have been licensed to pharmaceutical companies for further non-clinical and clinical development, and contributed

to innovation in treatments of intractable diseases. We aim to be a pioneer in the academia drug discovery in Japan to overcome sleep disorders.

1-3. Organization and Personnel

The basic concepts of the organization and the operation of IIIS involve creating a new style of research center by learning from the merits and virtues in the organization of “departments” in major US universities. In addition to the strong leadership of the “Department Head,” other characteristics including the flat organization, the appointment of Principal Investigators (PIs) regardless of their age and career stage, and flexible/dynamic allocation of the floor space and other resources to labs, have been consistently implemented.

The PI meeting chaired by the Center Director is held every month and serves as the decision-making body in IIIS. There are 8 labs operated by 12 PIs (4 Co-PIs) in the basic biology. One PI presides a pharmaceutical science lab with 3 assistant professors, and 3 PIs run 3 labs in experimental medicine. IIIS (core team) is thus comprised of 12 labs with 16 PIs and 14 non-PI faculties, 26 researchers, and 61 graduate/undergraduate students. IIIS attracts many students for their dissertation studies and the number of students is still increasing.

The IIIS Administration headed by the Administrative Director offers accounting and secretary services to PIs and assists the Center Director to operate IIIS in terms of personnel management, recruiting, budgeting, accounting, maintenance, grant application, outreach, public relations, etc. Further, it also functions as a local office of intellectual property right/legal/business development for alliances.

University of Tsukuba let IIIS organize its own personnel committee, which is chaired by the Center Director and comprised of 6 members including Dean of Faculty of Medicine, Provost of the Graduate School of Comprehensive Human Sciences, and Associate Dean of Biomedical Science, Faculty of Medicine. Decisions made by IIIS Personnel Committee are subjected to approval by Headquarters Personnel Council of the university.

1-4. Facilities and Equipment

The construction of the IIIS Building (6-stories with 8,000 m^2 of floor space) was completed in June 2015. It is located at the north corner of the Hospital Area, as shown in Appendix 3-4. The IIIS Building serves as a globally unrivaled venue for conducting interdisciplinary sleep research under one roof, covering 3 research fields of a) basic biology, b) pharmaceutical science and c) experimental medicine. It accommodates 2,600 m^2 of the vivarium exclusive to IIIS on the 5th and 6th floors, and the breeding area on the 6th floor accepts up to 6,000 individually ventilated cages, and there are 7 sleep recording labs and 6 behavior labs on the 5th floor, cementing its role as a leading global research resource.

In 2018, R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI), established as the joint project between Toyota Motor Corporation and University of Tsukuba in April 2017, moved into the unfurnished space (365 m^2) held for future expansion on the 4th floor of IIIS Building. We are starting a long-term collaboration of sleep measurement with F-MIRAI, using a Toyota fuel cell bus.

Expansion of the experimental medicine in IIIS had been a pending issue, and we thus newly established a facility for human sleep research, Human Sleep Lab in Innovation Medical Research Institute located in Kasuga Campus of the university as of March 31, 2019. This 211 m^2 wide facility near Tsukuba station has 4 beds of sleep measurement chambers, a bath room, and 1 bed of 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.

1-5. Financial Status

Yanagisawa’s grant of the Funding Program for World-Leading Innovation R&D on Science and Technology (FIRST) project started before the establishment of IIIS, helped the start-up of IIIS significantly. After its termination at the end of FY 2013, however, the total of external funds available for researchers in IIIS (core team) in FY 2014 was reduced to ¥178 M, and we ran short of research budgets. However, great efforts to raise research funds were made, and it increased rapidly as ¥282 M in FY 2015, ¥611 M in FY 2016, and ¥667 M in FY 2017. In FY 2018, it reached ¥770 M due to early-career PI’s efforts. The average amount of external funds/person in IIIS was ¥13,500,000, which was twice as large as the average in University of Tsukuba (¥6,120,000 in FY 2017). Since terms of many grants are multiple-years, we have already secured funding of ¥693 M in FY 2019, ¥505 M in FY 2020 and ¥291 M in FY 2021. We continue our efforts to acquire external funding every year to exceed the level of FY 2018.

2. Advancing Research of the Highest Global Level (within 12 pages)

2-1. Research results to date

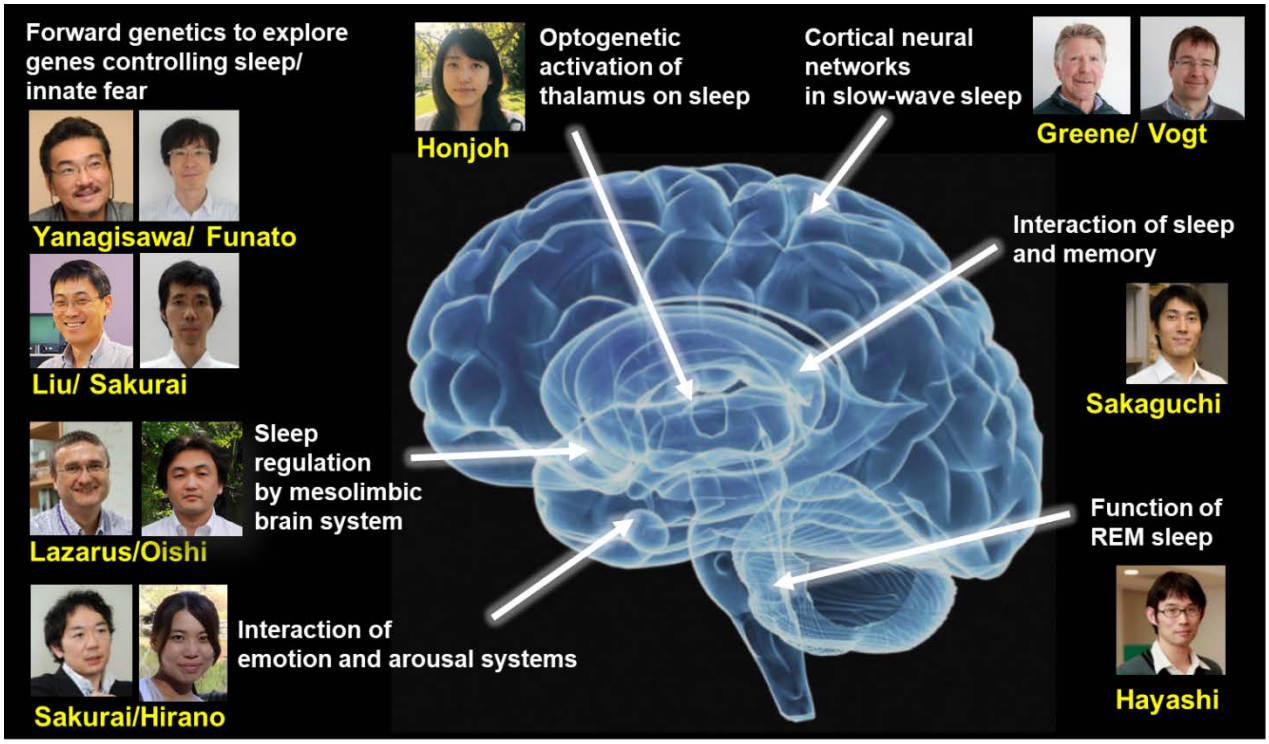
Describe issues of a global level that the Center has challenged, and give the results. Select 15 representative results achieved during the period from 2012 through March 2019. Number them [1] to [15] and provide a description of each. Place an asterisk (*) in front of those results that could only have been achieved by a WPI center and explain the reason in the description.

- In Appendix 1-1, list the papers underscoring each research achievement (up to 30 papers) and provide a description of each of their significance. And in Appendix 1-4 list the center's research papers published in 2018.

(1) 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.



(2) 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.

(3) 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] **Opening the black box of sleep homeostasis through large-scale forward genetics and phosphoproteomics**

How our brains achieve sleep homeostasis (i.e., sensing sleepiness and sleep longer/deeper when sleep is insufficient) remains a mystery. The neurobiological substrate for "sleepiness," or sleep need,

is completely unknown. Conceptually, the fundamental mechanism of sleep homeostasis constitutes a relaxation oscillator composed of a fast-acting sleep/wake switch and a slow integrator of sleep need. The wake state drives the integrator, which feeds back to the switch. New circuit-level experimental tools such as optogenetics have led to increasingly detailed understanding of the executive neural circuitry that constitutes the sleep/wake switch. However, essentially nothing is known as to how sleep need gradually accumulates during wakefulness and eventually drives the switch. In order to tackle this mystery, we launched a large-scale forward genetic screen of randomly mutagenized mice for sleep/wake abnormalities. In this non-hypothesis-based, unbiased exploratory approach, we screened more than 8,000 mice and identified: i) a gain-of-function mutation in the Sik3 protein kinase gene (Sleepy mutation) causing a marked increase in non-REM sleep amounts associated with a constitutively increased level of sleep need; and ii) a gain-of-function mutation in the Nalcn cation channel gene (Dreamless mutation) that causes a significant decrease in REM sleep amounts. We then carefully compared the whole-brain phospho-proteomic states of the Sleepy mutant mice and sleep-deprived mice, two distinct models of increased sleep need. We found that the cumulative levels of phosphorylation in a specific subset of mostly synaptic proteins gradually increase when sleep need accumulates, and their hyper-phosphorylated state is reversed when sleep need dissipates. These cumulative phosphostate changes may underlie both sleep homeostasis and synaptic homeostasis, the latter postulated as an important facet of sleep function. These paradigm-shifting achievements, representing a series of collaborations among multiple IIIS core labs and satellites, would have been utterly impossible without the amount and quality of scientific resources, as well as the highly interactive environment uniquely provided by the WPI-IIIS.

* [2] **The functions of REM sleep revealed from chemogenetic approaches**

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. REM sleep inhibition by forced awakening is not an effective way to address the function of REM sleep, because the stimulus itself causes extreme stress. Therefore, to elucidate the function of REM sleep, alternative approaches were necessary. First, 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. This was accomplished by a technique called chemogenetics, a novel technique that allows manipulation of neuronal activity. 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 used a device that reduces REM sleep. Furthermore, combining with chemogenetics, it was 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.

* [3] **Deciphering neuronal circuits linking the limbic system, hypothalamus, and brain stem**

Sleep/wakefulness states have long been thought to be regulated by two major processes, i.e., circadian rhythm and sleep pressure. In the two-process model of sleep regulation, the sleep-wake cycle is driven by a gradually increasing sleep load or sleep pressure, that is being concurrently opposed by alerting signals generated by the circadian clock. However, sleep/wakefulness states are also obviously influenced by other allostatic factors, such as nutritional state and emotion. However, the mechanism by which the systems that regulate mood and/or emotion alter sleep/wakefulness states had not been identified so far. To depict neuronal circuits of this function, with combination of viral tracings and optogenetic/pharmacogenetic experiments, we identified structural and functional connectivity between the limbic system, hypothalamic arousal-related neurons, and monoaminergic cells in the brain stem. These works revealed the mechanisms by which the limbic system and monoaminergic systems regulate sleep/wakefulness states, and would help us understand pathophysiology of insomnia, in which anxiety and mood play a prominent role.

* [4] **Experimental dissociation of sleep homeostasis and emotionally/motivationally induced wakefulness**

The classical “two-process model” of sleep regulation dictates that sleepiness is influenced by two major processes: homeostatic and circadian. However, it is obvious from our daily experience that sleepiness can also be acutely suppressed by emotional/motivational stimuli (here termed “arousal”).

This study demonstrates that arousal and sleep homeostasis are indeed dissociable from each other by behavioral and biochemical criteria. This conceptual distinction turns out to be extremely important: it made a strong basis for later studies in multiple labs at WPI-IIIS, e.g., characterization of the Sleepy mutants having defects in the dissipation of homeostatic sleep need but not in motivational arousal (Yanagisawa/Funato lab, Achievement [1]); and the precise dissection of a neuronal circuit inducing motivational arousal, which is not directly influenced by homeostatic sleep need (Lazarus/Oishi lab, Achievement [5]).

* [5] **The brain mechanism underlying the desire to sleep in boring situations**

As humans, we often defy sleepiness and stay awake when attention is necessary, but also experience an inescapable desire to sleep in boring or pleasureless situations. The brain mechanisms governing the regulation of sleep by cognitive and emotional factors are not well understood. Michael Lazarus previously demonstrated that the arousing effect of caffeine, the most consumed psychoactive compound in the world, is abolished in rodents with site-specific deletion of adenosine A_{2A} receptors in the nucleus accumbens – a part of the brain that is associated with motivation and pleasure. Recently, the Lazarus Lab also revealed that the nucleus accumbens can produce sleep. The findings may explain why we have the tendency to fall asleep in the absence of motivating stimuli, i.e., when bored. The achievement has initiated a new area of sleep research on hedonic motivation as a major sleep-gating factor (Lazarus M., et al. Trends Neurosci, 2012, 35:723). The teleological problem of sleep function arises from the presumption of sleep's evolution from a default state of waking. Humans are likely biased towards this presumption by the egocentricity of waking consciousness. The achievement, however, provides further evidence that sleep is the brain's default state that is established in the absence of arousing inputs. Finally, the newly identified sleep circuit may open new therapeutic avenues for treating insomnia and other sleep or psychiatric disorders.

[6] **Elucidation of the functions of thalamic matrix cells in regulation of cortical activity and arousal**

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 demonstrated that a thalamic neural subpopulation, matrix cells, promotes behavioral arousal through global cortical activation. The results provide the direct evidence for the role of thalamus in arousal. Importantly, we also showed that activation of somatosensory thalamic nucleus does not promote arousal, suggesting that decreased sensory input per se cannot account for sleep. This research not only deepens understanding of thalamocortical mechanisms in wake/sleep regulation, but may lead to the development of treatments for the recovery of consciousness and improved cognitive function in the future.

* [7] **Understanding the biological clock regulating sleep/wake rhythms at cellular and molecular levels**

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) and that Neuromedin S neurons are essential to generate sleep rhythms (Lee et al., Neuron). 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., PNAS). 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). Our studies focusing on the circadian clock have advanced the understanding how the biological clock regulates sleep and metabolism, potentially leading to clinical applications.

* [8] **Applying the functional connections between sleep and memory for future therapy**

Memory is largely affected by sleep. Through understanding the interaction mechanisms, we may be able to contribute to creating a new therapy. Indeed, we found critical circuits that connect memory and sleep; the orexinergic neurons in the hypothalamus, which are essential for maintaining vigilance, control memory expression via locus coeruleus noradrenergic neurons (3). On the contrary to the conventional view of the noradrenergic function in memory, we provide evidence that the dopaminergic neurons in the locus coeruleus play critical roles in a novelty effect on memory consolidation (1). As a preliminary approach to apply the findings to bedsides, we succeeded to lower the fear memory response by cueing the mice with memory-related sound during memory consolidation period in NREM sleep, showing a possibility to treat PTSD patients by sound (2). These can be only achieved by IIIS scientists, who lead the field of sleep research (e.g., identified orexin) with broad international collaboration, integrative mind with medicine (holding 11 MDs in the center) and cutting-edge technology including virus-mediated connectome analysis and optogenetic intervention.

* [9] **Orexin to locus coeruleus pathway gates fear-related behavior.**

Fear is an important physiological function for survival. The amygdala has been shown to play an important role in regulation of fear. Hypothalamic orexin neurons are activated by fearful stimuli to evoke a 'defense reaction' with an increase in arousal level and sympathetic outflow to deal with the imminent danger. However, how this system contributes to the emergence of fear-related behavior had not been well understood. Orexin neurons in the hypothalamus send excitatory innervations to noradrenergic neurons in the locus coeruleus (NALC) which express orexin receptor 1 (OX_1R) and send projections to the lateral amygdala (LA). Inhibition of this di-synaptic orexin → NALC → LA pathway by pharmacological or opto/chemogenetic methods reduced cue-induced fear expression. Excitatory manipulation of this pathway increased a fear-related behavior only when the environment contains some elements suggestive of danger. Although, fear memory helps animals respond to a context or cue previously paired with an aversive stimulus, fear-related behavior is sometimes evoked even in a distinct context containing some similar elements, which is known as fear generalization. Our observation suggests that the orexin → NALC → LA pathway might contribute to this response. This work suggested the potential effectiveness of orexin receptor antagonists for treating excessive fear response or overgeneralization seen in anxiety disorder and post-traumatic stress disorder (PTSD).

* [10] **A forward genetics screen to uncover the molecular basis of innate fear in mice**

Emotions are innate and powerful drivers of animal behaviors; and yet little is known about the molecular basis of emotion. Here, we developed the first forward genetics (from phenotypes to genes) screen on emotion to investigate the molecular basis of innate fear. A novel design of this recessive screen is the ability to rapidly identify the causative mutations of mutant mice after phenotypic screening. We found that mutation of the Trpa1 gene, which encodes a pungency/irritancy receptor, diminished 2MT/TMT and snake skin-evoked innate fear behaviors, such as freezing. Moreover, we found that Trpa1 expressed in the trigeminal neurons could act as a novel chemosensor to detect predator odors. Our results substantiate the utility of a forward genetics approach to investigate the molecular mechanisms of innate fear and perhaps fear/anxiety-related human diseases.

* [11] **Essential yet distinct roles of adenosine A_1 and A_{2A} receptors in sleep gating and function**

As knowledge of the molecular and circuit bases of sleep/wake regulation expands, new roles of adenosine receptors in modulating different aspects of sleep emerge. WPI center PIs Michael Lazarus and Robert Greene are leading experts on the role of the classic somnogen adenosine and proposing a new model of sleep-wake regulation in which adenosine receptors influence sleep/waking behavior by modulating arousal level through adenosine A_{2A} receptors ($A_{2A}R$) and sleep need through adenosine A_1 receptors (A_1R). Increased activity of the arousal centers promotes wake. For example, activation of $A_{2A}R$ in the nucleus accumbens and hypothalamus facilitates sleep through the inhibition of arousal promoting neurons. The duration of waking time positively correlates with sleep need and the buildup of extracellular adenosine. The buildup of adenosine in the cortex and thalamus increases slow-wave activity, which is widely used as a marker of mammalian sleep homeostasis, through activation of A_1R. The sleep state is permissive for sleep function which resolves sleep need (as sleep function is accomplished) as marked by the resolution of rebound slow-wave activity.

[12] **Clarification of a mystery to scratch skin on feeling itch: Role of spinal dynorphin**

This study describes that a specific population of spinal inhibitory interneurons (B5-I neurons) inhibits itch sensation induced by pruritic agents and endogenous kappa opioid peptide dynorphin is a key neuromodulator of biological defense system on pruritus sensation. Additionally, unlike other existing antipruritic drugs, nalfurafine effectively reduces the itch sensation induced by several pruritic agents and deletion of B5-I neurons. Thus, this study provides a new cellular basis for the itch sensation and strongly suggests that kappa opioid agonists may be a broadly effective therapy for pathological itching. Recently many researchers have been curious about a mystery that dynorphin is co-localized with orexin in the same synaptic vesicle of neurons in the brain and is also simultaneously released with orexin into the synaptic cleft. Present study might provide a clue to clear up the mystery that is coexistence of inhibitory peptide dynorphin and excitatory peptide orexin.

* [13] **Detailed description of energy metabolism during human sleep**

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 describe characteristic phenotype of sleeping energy metabolism. 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 prior to awakening. 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.

* [14] **The mechanistic therapy of narcolepsy: proof-of-concept**

Narcolepsy is an intractable disease of daytime sleepiness, caused by a deficiency of the wake-promoting neuropeptide orexin. Narcolepsy patients exhibit highly unstable sleep/wake state transitions; pathological intrusions of non-REM and REM mechanisms into wakefulness result in characteristic non-REM-related symptoms (e.g., “sleep attacks”) and REM-related symptoms (e.g. cataplexy, or a sudden loss of muscle tone; and hallucinations when waking up or going into sleep). A majority of patients with these typical symptoms lacks detectable levels of orexin, due to a selective loss of orexin-producing neurons in the hypothalamus. In orexin-deficient mouse models, cerebroventricular administration of orexin ameliorates the disease, showing that their orexin receptors and downstream signaling pathways are intact. However, since the orexin peptide does not penetrate the blood-brain barrier, orexin replacement therapy requires either i) development of small-molecule, CNS-accessible orexin receptor agonists, or ii) central administration of orexin in a clinically feasible manner. Through years of collaborations among IIIS core labs and its Akita satellite, we have achieved proof-of-concept for both of these strategies. The resources and environment provided by WPI-IIIS, that enabled a close interaction of medicinal chemistry and pharmacology teams was essential for the effort.

* [15] **The neuropeptide orexin as a potential anti-inflammatory therapeutic for septic shock**

Regulation of immune responses by the brain gains much attention in recent years. Septic shock is the most serious form of sepsis, a systemic inflammatory response to infection. Due to the lack of effective treatments, it remains the most common cause of death in intensive care units. Under sepsis, the systemic inflammation causes permeabilization of the blood-brain barrier. In this study, we show that peripheral injection of orexin unexpectedly improves survival in a mouse model of severe septic shock. We further show that orexin peptide penetrates into and acts directly in the brain under sepsis to exert a pleiotropic anti-inflammatory effect. Peripheral orexin administration may prove to be a novel therapy for septic shock, which takes advantage of the pathophysiology of sepsis. This exploratory study is enabled by the highly interactive environment at WPI-IIIS, which enabled a flexible collaboration between two IIIS core labs.

2-2. Research environment including facilities and equipment

Describe the degree to which the Center has prepared a research environment appropriate for a world premier international research center, including facilities, equipment and support systems, and describe the functionality of that environment.

The development of the facilities has been continuously moving forward along with our progress plan.

Human Sleep Lab is about to be launched soon at Innovation Medical Research Institute which is located in Kasuga Campus of the university. The human calorimeter that used to be on the 3rd floor in IIIS Building had already been moved to the new location and four sleep chambers, shower room and lavatory have been installed to Human Sleep Lab. It will make possible for us to conduct sleep measurement on five people in parallel and significantly accelerate our studies on experimental medicine.

The space left after moving out the human calorimeter, we are planning to invite a new PI who studies molecular genetics of sleep using fruit flies (drosophila). We will set up a new lab with all the equipment that is required for the sleep research using flies, including a dark chamber with a precise air-conditioning system and Drosophila Activity Monitors (DAM) system, a number of incubators for fly cultures, and a fully functional lab for fly manipulations under the dissection microscopes and molecular biology. With such systems, a full range of sleep studies using Drosophila such as non-biased genetic screens and electrophysiology with patch clamp could be performed for further expansion of neuroscience study in IIIS.

2-3. Competitive and other funding

Describe the results of the Center's researchers to date in securing competitive and other research funding.

- In Appendix 3-6, describe the transition in acquiring research project funding.

Since most of the PIs in IIIS (core team) were invited from the outside University of Tsukuba, not much 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. The total amount of the funds executed each year has been growing as ¥1.5 M in FY 2012, ¥63.8 M in FY 2013, ¥178 M in FY 2014, ¥282 M in FY 2015, ¥611 M in FY 2016 and ¥667 M in FY 2017. In FY 2018, it has reached ¥770 M, more than 500 fold of the funding in the 1st year.

Particularly in FY 2018, early-career PIs gained newly large-scale funds such as AMED-CREST, PRIME, Brain/MINDS project (AMED), PRESTO (JST), etc. Their efforts contributed to the significant increase of the commissioned research projects from the government agencies (¥24 M (FY 2013), ¥43 M (FY 2014), ¥40 M (FY 2015), ¥165 M (FY 2016), ¥174 M (FY 2017) and 276 M (FY 2018)). Grants-in Aid for Scientific Research (JSPS) are the funds which are important for research institutions conducting fundamental studies like IIIS, and we encourage all the qualified faculties and researchers to apply for them. The sum of the funds executed each year has been increasing steadily; ¥0.87 M (FY 2012), ¥23 M (FY 2013), ¥102 M (FY 2014), ¥116 M (FY 2015), ¥286 M (FY 2016), ¥352 M (FY 2017) and ¥344 M (FY 2018).

University of Tsukuba awards small prizes to faculties who acquired large funds. In FY 2018, 6 PIs were honored for their achievements of acquiring large funds, though there were only 131 award winners among total 1,864 faculty members in the university. Additionally, the average amount of external research funds in IIIS was ¥13.5 M in FY 2018. This was more than twice the average in the university, ¥6.1 M (FY 2017 data).

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 2018.

2-4. State of joint research

Describe the results of joint research conducted with other research organizations both in and outside Japan.

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 (Satellite)

From FY 2013 to FY 2017, we conducted collaboration with Tetsuo Shimizu, the psychiatrist in Akita University Graduate School of Medicine under the research collaboration agreement, which covered the collaboration in the pathological study of sleep disorders such as narcolepsy and human genetics. In the human genetics, we focused on screening for individuals of true short sleeper and their families for human genetic studies to identify one family.

After Shimizu's retirement at the mandatory age, we conclude collaborative research agreement with his successor, Kazuo Mishima in October, 2018. We expect fruitful collaboration with him on the translational research in sleep medicine such as analysis of the BioBank repository he collected from sleep

disorder patients and studies using the Mobile Sleep Lab or wearable sleep measurement devices in future.

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

We conducted a joint project with the Hospital Management Division of Ibaraki Prefecture intended to promote clinical research into sleep disorders and to establish a sleep medical center. A medical specialist of sleep apnea syndrome, Satoh was jointly appointed to PI in IIIS and the director at Ibaraki Prefectural Medical Center of Psychiatry from April 2015 to March 2016. After he came back to IIIS, we looked for his successor but could not find a good candidate. Fortunately, we recently succeeded in recruiting Takashi Kanbayashi and Hideaki Kondo from Akita University Graduate School of Medicine and Department of General Medicine, Nagasaki University Hospital, respectively. They will continue the translational research such as the diagnosis and pathophysiological study on hypersomnia patients such as narcolepsy, and development of the treatment to the orthostatic syncope with a sleep aspect retreat syndrome with sleep disorder. They also will be involved in the development of the sleep measurement services and AI software for diagnosis of sleep disorders in collaboration with S'UIMIN Inc.

(3) Graduate School of Pharmaceutical Sciences, Kyoto University (Satellite)

In July 2015, we installed Hitoshi Okamura, the Department of System Biology, Kyoto University Graduate School of Pharmaceutical Sciences as a Satellite PI, and concluded a collaborative research agreement. The objective of this collaboration is to fish out genes regulating jet-lag by ENU mutagenesis screening. Due to a malfunction of cage/rack system to monitor behaviors of mice, the collaboration has been suspended but will be resumed shortly.

(4) RIKEN Brain Science Institute

From FY 2014 to FY 2018, Hayashi had been conducting joint research with Dr. Shigeyoshi Itohara, Laboratory for Behavioral Genetics, RIKEN Brain Science Institute, on the study to elucidate the physiological significance of sleep toward developing treatments for mental disorders. The function of REM sleep is one of the largest mysteries in neuroscience. To address the roles of REM sleep, we have been aiming to establish mouse models in which REM sleep can be manipulated. We identified neurons in the brainstem pons that strongly inhibit REM sleep. DREADD-activation of these neurons allowed manipulation of REM sleep for several hours, and as a result, it was revealed that REM sleep has a role to increase slow wave activity in the subsequent non-REM sleep (Hayashi et al., Science, 2015)

(5) JAXA Space Biomedical Research Office

The Grants-in-Aid for Scientific Research on an Innovative Area: "Integral Understanding of Life Regulation Mechanism from Space," which was jointly applied for by 11 groups including IIIS, featuring Astronaut Dr. Satoshi Furukawa as Head of the Scientific Research on Innovative Areas, was adopted in FY 2015. While we develop AI software for sleep staging by analysis of EEG and conduct a clinical research evaluating effect of insomnia treatment drugs on physical/cognitive functions in this project, we also participated in the closed-environment stress test conducted in the isolation/confinement facility in JAXA, taking charge of sleep diagnosis.

(6) The Jikei University

From April 2015, we conducted a joint research with Dr. Megumi Shimoyama at the Jikei University to study the effect of an orexin agonist on the sleepiness side effect of morphine. Opioids are potent analgesics used in patients with acute and chronic pain, but sedation is one of the major dose-limiting side-effects of opioids. There are no useful drugs against this side-effect in medical practice. In the collaboration, we found that, in rats received intraperitoneal administration of the orexin agonist, YNT-185 concurrently with subcutaneous administration of morphine, EEG slow-wave bursts associated with behavioral stupor were attenuated effectively. We jointly filed the patent application on the potential of orexin agonist, YNT-185, for the alleviation of morphine-induced sedation and published the original paper at Analgesia.

(7) R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI)

When we built IIIS Building, we reserved the half (the south side) of the 4th floor unfinished as a future expansion space. In June 2017, R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI) supported by Toyota Motor Corporation decided to move into the future expansion space. F-MIRAI led by Dr. Isamu Takahara is the joint project between Toyota and University of Tsukuba starting from April 2017, to develop fundamental technologies for regional communities to realize Society 5.0,

to develop social measurements by applying Internet of Things (IoT), and to resolve the social engineering issues through the big data analysis by artificial intelligence.

They implemented their office and an operation room in FY 2017 and FY 2018, respectively. We started actual collaboration from October, 2018, and developed a wearable sleep measurement device, which was manufactured by NeuroSky Co. In FY 2019, as the next step, we are developing the Mobile Sleep Lab based on a fuel cell bus lent by Toyota at no charge, taking advantage of its characteristics. The fuel cell bus can supply bulk power for air conditioning and sleep measurement without noise and vibration, and access easily to subjects at living/working environment.

2-5. Appraisal by society and scientific organizations

Describe how society and/or scientific organizations in and outside Japan have recognized the Center's research achievements.

- To substantiate the above evaluation, list the main awards received and invitational/Keynote lectures given by the Center's researchers in Appendix 1-3.

The research achievements of IIIS are highly recognized in and outside Japan, and IIIS researchers have received many awards. For example, Yanagisawa has received many prestigious academic awards from around the world such as Jokichi Takamine Memorial Award (2013), the Walter B. Cannon Memorial Award (2015), Erwin von Bälz Preis (2017), and the Keio Medical Science Prize (2018), for his contribution to revolutionizing vascular biology and sleep medicine by the discovery of endothelin and orexin. Since endothelin and orexin served as drug targets of pulmonary hypertension and insomnia, respectively, the contributions to public health were also appreciated. In recent years, he was also commended for his contribution to the development of culture and society through the sleep research and received several awards which are well known to general public such as Medal with Purple Ribbon (2016) and the Asahi Prize (2018). This shows that our efforts to approach sleep related social problems through elucidation of the mysteries of sleep are widely recognized among general public.

T. Sakurai received the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology (2013) and Shiono Prize (2017) for the discovery of orexin and the elucidation of its physiological functions. Nagase has been highly evaluated for his contribution to drug discovery, such as the design and synthesis of the first κ opioid receptor specific agonist, nalfurafine, and received the Okochi Memorial Technology Prize (2013), National Commendation for Invention – the Invention Prize (2013), and Yamazaki Teiichi Prize (2014). Moreover, other PIs, non-PI faculties, postdocs, and graduate students have also been recognized for their outstanding achievements by various academic organizations, and the number of awards received so far exceeds 50 in total since the establishment of IIIS.

With regard to invitational/keynote lectures, all PIs have been invited as speakers and they have given more than 300 lectures at domestic and international conferences so far. Along with lots of awards received so far, it reflects high acclaim from research communities for IIIS, which further enhances the recognition of IIIS as a world-leading research institute specializing in fundamental sleep research.

It has been decided that the Center Director will be appointed to the Chairman of "The 45th Annual Meeting of Japanese Society of Sleep Research" in 2020 to be held in Yokohama. He will also be appointed to a member of the Steering Committee of Gordon Research Conference of Sleep Regulation and Function in 2020 to be held at Hotel Galvez in Italy. We expect that the domestic/international visibility of IIIS will be further boosted.

We believe that we would be able to continue to raise remarkable achievements and enhance our presence in research communities by maintaining the environment in which researchers and students can vigorously communicate and fully demonstrate their abilities. Furthermore, we aim to contribute to society by actively disseminating our latest research achievements and information on sleep and health to general public.

2-6. Feeding Research Outcomes Back into Society

2-6-1. Applications of research results

Describe the applications created from research results, their effect in spawning innovation, intellectual properties (IPs) obtained, and joint research activities conducted with corporations, etc.

(1) Patent applications

We filed 18 patent applications as listed in the following table. The applications are all commensurate with the research strategy of IIIS, which involves elucidating the sleep/wake regulation mechanism and the pathogenesis of sleep disorders, and developing new treatment methods. Due to the nature of our research subjects, sleep science, the major means of practical application of research results include licensing of patents to pharmaceutical/diagnosis companies. At present, patent No. 12

in the table was licensed to Nippon Chemiphar and they have been examining the feasibility of its medical application. We are engaging in negotiation with multiple companies for licensing.

No.	Title of invention	Inventor	Date	Application number
1	Sulfonamide derivative or its pharmaceutically acceptable acid addition salt	Nagase H, Nagahara T	Dec 12, 2013	Patent application 2013-257523
2	Preventive remedy for septicemia	Irukayama Y, Yanagisawa M, Ogawa Y	Mar 28, 2014	Patent application 2014-067451
3	Nalfurafine containing preparation for topical application	Nagase H, Saiki K, Shimoyama J, Tada M	Sep 30, 2014	Patent application 2014-201237
4	Orexin receptor antagonist	Nagase H, Irukayama Y, Ogawa Y, Miyamoto M, Nitta K	Oct 31, 2014	Patent application 2014-222969
5	Sulfonamide derivative or its pharmaceutically acceptable acid addition salt	Yanagisawa M, Nagase H, Irukayama Y, Saito T	Feb 19, 2015	Patent application 2015-031041
6	Morphinan derivative	Nagase H, Fujii H, Saito A, Nakata E, Hirose M, Oi I, Hayashida K	Mar 17, 2015	Patent application 2015- 54079
7	Sulfonamide derivative or its pharmaceutically acceptable acid addition salt	Nagase H, Yanagisawa M, Saito T, Kutsumura N, Irukayama Y	Jun 12, 2015	Patent application 2015-119785
8	Nalfurafine containing transdermal absorption cataplasm	Nagase H, Tada M, Yashima M, Saiki K	Jun 24, 2015	Patent application 2015-126282
9	Sleep state automatic judgment system and judging method in consideration of individual difference	Yanagisawa M, Satoh M	Oct 28, 2015	US provisional application (Application #: 62/247,329)
10	Morphinan derivative and its medical use	Nagase H, Yamamoto N, Irukayama Y, Saito T	Oct 29, 2015	Patent application 2015-212553
11	Morphinan derivative and its medical use	Nagase H, Yamamoto N, Irukayama Y, Saito T, Yanagisawa M, Nagumo Y	Aug 9, 2016	Patent application 2016-155477
12	Morphinan derivative and its medical use for opioid δ receptor related disease	Nagase H, Fujii H, Saito M, Nakata E, Hirose M, Ooi S, Hayashida K	Sep 16, 2016	Patent application 2016-203925
13	Novel slow-wave sleep-inducing agent	Lazarus M, Saito T, Nagase H, Korkutata M,	Oct 18, 2017	Patent application 2017-202225
14	Morphinan derivatives	Nagase H, Yamamoto N, Watanabe G, Mogi Y	Aug 31, 2017	Patent application 2017-166577
15	The prevention of the sleepiness with the pain-killer	Nagase H, Yanagisawa M, Saito T, Shimoyama M	Dec 7, 2017	Patent application 2017-235529
16	Sleep improve reagent	Nagata N, Fukudome S, Kikuchi Y, Makita M, Nakayama Y, Inagawa H	July 21, 2017	Patent application 2017-141672
17	Sulfonamide derivative or its pharmaceutically acceptable acid addition salt	Nagase H, Yanagisawa M, Saito T, Irukayama Y	Dec 12, 2017	Patent application 2017-238093

(2) Joint research with companies

The joint research projects between IIIS and the companies described below, also aimed at 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 on sleep-aiding products in collaboration with companies/research institutions.

A Global Pharmaceutical Company

From April 2015 through December 2018, we performed a joint research with the company with the purpose of developing a CNS drug. The goal was to deliver groundbreaking eradicative medicine to patients suffering from a sleep disorder by accelerating the structure optimization of the lead compound we developed. In this joint research, IIIS took charge of medicinal chemistry and pharmacology, while the company took their share of pharmacokinetics and toxicology. We identified a promising development candidate with reasonable physicochemical properties and filed the patent application

covering it independently from the company. They, however, decided not to proceed with the candidate to the non-clinical development, since they preferred their own compounds they found in their discovery research. We thus finished the joint research in December 2018. We looked for an alternative partner of the non-clinical development, and Mitsubishi Tanabe Pharmaceutical Corp. has been performing several preclinical studies.

Sumitomo Dainippon Pharma Co., Ltd.

From April 2016 through March 2019, we performed an exploratory study of the treatment for REM sleep behavior disorder (RBD) using our original RBD model mouse with Sumitomo Dainippon Pharma. We screened and evaluated compounds of Sumitomo Dainippon Pharma using this model, which has been validated with clonazepam and an orexin antagonist. As a result, we successfully found several drugs with different target molecules, which ameliorated the RBD phenotype.

Furthermore, in February 2019, we started another collaborative project on the drug repositioning. We estimate the marketed drug for the development as hypersomnia therapeutic drug using the narcolepsy model mice or Sleepy mice, since they already had preliminary results showing improvement in the wakefulness.

Fujifilm Corporation

From 2013 to 2015, we engaged in the joint research of pharmacokinetics of the sleep-improving ingredient and elucidation of a sleep-inducing mechanism with Fujifilm and found the sleep-inducing action of zinc. This results have been already implemented as a product marketed by them, the sleep-aiding supplement “Suttone.”

Since April 2016, we have been performing drug discovery collaboration using the compound library established by Nagase.

In addition to these collaborations, we have licensed the orexin2 receptor agonist, YNT-185 and the orexin 1 receptor antagonist, YNT-1310 as research reagents to Wako Pure Chemicals, the subsidiary of Fujifilm.

Toray Chemical Industries, Ltd

Since May 2014, we have been conducting the ongoing joint research with Toray to elucidate the sleep modulating activity of Narfulafin related compounds. Through this joint research, we discovered novel orexin 1 receptor antagonist, YNT-1310 having morphinan structure, and filed several patents. We are in negotiation with several companies for the collaboration of structure optimization.

We also performed additional collaboration on discovery of the drug with anti-malaria activity.

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. Although experiences on a daily basis reaffirm the significant impact of bedding on sleep, given the lack of scientific research and validation, we aimed to objectively evaluate the effect of body-pressure dispersion of a mattress on sleep. We conducted a randomized crossover study of mattresses showing different body-pressure dispersions by means of polysomnography. A mattress commonly used in the medical institution was used as the control, and a mattress designed for higher body-pressure dispersion (a functional mattress) was used for the intervention. In the crossover study, there were significantly fewer SWS episodes with the functional mattress than with the control mattress and longer SWS episode duration with the functional mattress than with the control mattress. The prolonged slow wave sleep induced by the higher body-pressure dispersion may contribute to the better recovery from the fatigue in the sleep.

Mitsubishi Tanabe Pharmaceutical Co., Ltd.

In FY 2018, we collaborated with Mitsubishi Tanabe to evaluate efficacy of their compound on narcolepsy using orexin KO mice. It showed a wake promoting activity but the effect is not enough for further development.

S’UIMIN Inc.

S’UIMIN Inc. was established as a business sector of IIIS in October 2017, nominating Dr. Masaaki Fujiwara, ex-CEO of Chiome Bioscience Inc., and Yanagisawa to the joint representatives. S’UIMIN means “sleep” in Japanese and stands for “Sleep is Ultimate Intelligent Mechanism In Nature” as well. Major missions of S’UIMIN are to implement translational researches such as the development of a

sleep measuring system for diagnosis, as well as to facilitate licensing of research tools/lead compounds of novel drugs created in IIIS to pharmaceutical companies as a private TLO. S'UIMIN should take advantage of business seeds of IIIS to make profits, which should be fed back to IIIS to support future studies and reproduce new business seeds.

Kyocera Cooperation

In FY 2018, we made a preliminary study of the sleep staging with Kyocera's earphone-type sensing device under MTA. We confirmed that it could detect blood stream and vaso-motion by Doppler effect and identified the amplitude of vaso-motion showing a clear difference between wake and sleep stages. We thus started the official collaboration and had the kick off meeting in April 2019. We expect that this collaboration continues three years step by step with enough research funding for clinical studies using normal subjects for the device development and validation. It is a very challenging approach to apply the blood measuring device for sleep staging, but we anticipate synergy with S'UIMIN's sleep measurement service by using the wearable EEG measuring device.

2-6-2. Achievements of Center's outreach activities

* Describe what was accomplished in the center's outreach activities during the period from 2012 through March 2019 and how the activities have contributed to enhancing the center's "globally visibility." In Appendix 5, describe the concrete contents of these outreach activities and media reports or coverage of the activities.

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

In order to enhance the visibility of IIIS, we have held lots of outreach events. One of the most outstanding events in the past seven years was the 6th WPI Science Symposium which we organized as a host institute in 2017. Setting two venues targeting different ages, we provided a wide variety of activities such as panel discussions, cross talk sessions, science café, comedy shows, and quiz rallies. The event was concluded in great success with more than 800 onsite visitors and 16,000 live broadcast viewers on Nico Nico Live, which was the largest number of participants in the past WPI symposia.

Since 2012, we have held workshops and events of science café every year targeting adults who are interested in sleep or have some trouble with sleep. For example, in 2017, we held a workshop with Yanagisawa sponsored by Hibiya Library in Tokyo. As a guest speaker, we invited a high school student who suffered from narcolepsy and asked him to share his experiences as a patient. Greatly influenced by Yanagisawa, after the workshop he studied very hard and succeeded in passing the entrance examination to a medical school. As a medical student, he reunited with Yanagisawa in March 2019, and this story was reported in the Asahi Shimbun and had a great response. Moreover, not only organizing the outreach events, we have also participated in many science events such as the Super Science High School (SSH) Annual Research Meeting, AAAS Annual Meeting and WPI Science Symposium every year.

For IIIS researchers and PR staffs, these events have offered great opportunities not only to introduce our research achievement, but also to know reactions to our sleep research through dialogue with general public.

(2) Development of new approach for outreach: Nico Nico Live

As events to introduce our studies and facility to general public, we broadcasted two Nico Nico Live programs. In the programs, lots of researchers including Yanagisawa, T. Sakurai, other PIs and students at IIIS introduced cutting-edge sleep science and their own studies, interacting with viewers through real-time comments. Furthermore, we held virtual tours of IIIS Building to introduce our labs and research facilities, which had not been generally open to the public. The total numbers of viewers in the programs were about 20,000 (2 hour-program on January 29, 2018) and 116,000 (36 hour-program on May 28-29, 2018). In the both programs, more than 95% of the viewers answered "enjoyed" in the questionnaire taken at the ending. The programs showed a great potential of the new interactive outreach activities via internet broadcasting.

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

In order to attract interest in scientific research and develop the next generation of scientists, we have been actively accepting visitors from junior/senior high schools and colleges since the establishment of IIIS. The number of domestic and foreign schools delegating students and teachers to IIIS was more than 60, and we offered various kinds of the educational program such as lectures, demonstration of experiments, round-table talks with researchers, workshops about scientific literacy, lab tours, and so on. Especially, students of Uto High School in Kumamoto visit IIIS on a regular basis (twice a year) and learn sleep researches as well as the importance of sleep. After the lecture by

Yanagisawa, they autonomously discussed adolescent-specific sleep problems and decided to take a nap called “Uto Uto Time” after lunch in order to make up for their lack of sleep. They went along with this idea to stop extracurricular activities in the morning. This is a great example of the achievement of our outreach activities to encourage students to reconsider their sleep issues from a scientific point of view.

(4) Media Coverages

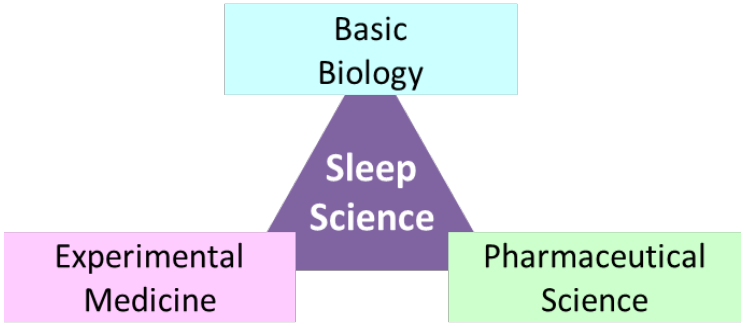
The appearance of IIIS on the media including newspapers, magazines and TV shows has been increasing year by year. In FY 2018, the number of media coverage was the highest on record, i.e., 180, which was about 1.7 times as many as that of FY 2017. The press releases on the research achievements of IIIS have attracted great interest from the media, and in particular at least 64 media reported the achievement published in Nature, which suggested the biochemical substance of sleepiness.

Various overseas media such as “National Geographic,” “The Atlantic,” “Quanta Magazine” and “Nature Index” have also covered IIIS and its achievements, and the international recognition of IIIS has been increased.

3. Generating Fused Disciplines (within 3 pages)

3-1. State of strategic (or "top-down") undertakings toward creating new interdisciplinary domains

The 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 shown in 1-2. 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.

In FY 2018, to reinforce research capabilities of the team, especially in experimental medicine, a new facility for studies of human sleep, Human Sleep Lab was built in the COI Building located 1 mile south of IIIS. The Human Sleep Lab is the facility of 211 m^2 wide and accommodates 4 sleep-chambers, a bath room, the human calorimeter moved from IIIS Building, and offices. Further, for the collaboration with Ibaraki Prefecture, 2 medical specialists for sleep, Kanbayashi and Kondo were recruited from Akita University Graduate School of Medicine and Department of General Medicine, Nagasaki University Hospital, respectively. As of April 1, 2019, Kanbayashi has been appointed to PI/Professor and Kondo to Associate Professor in Kanbayashi lab. They are supposed to be engaged partially in clinical studies/services at Ibaraki Prefectural Medical Center of Psychiatry. Opening Human Sleep Lab and the appointment of 2 clinical investigators improved our capability of human research significantly and expanded opportunities of collaboration with other research fields.

To strengthen pharmaceutical science in the team, since January 2019, we have commenced collaboration with Mitsubishi Tanabe Pharma Corporation, who took over development of a CNS drug from another pharmaceutical company. In the collaboration with the company since September 2015, we succeeded in the optimization of a lead compound to identify a candidate for non-clinical development aiming to the causal therapy of narcolepsy. They, however, decided not to proceed with our candidate compound to the non-clinical development, since they preferred their own compounds they found in their discovery research. We thus looked for an alternative partner of the non-clinical development at the workshop of Drug Seeds Alliance Network Japan in Osaka and BIO-Europe in Copenhagen, and Mitsubishi approached us after BIO-Europe. We agreed to let them perform the initial step of non-

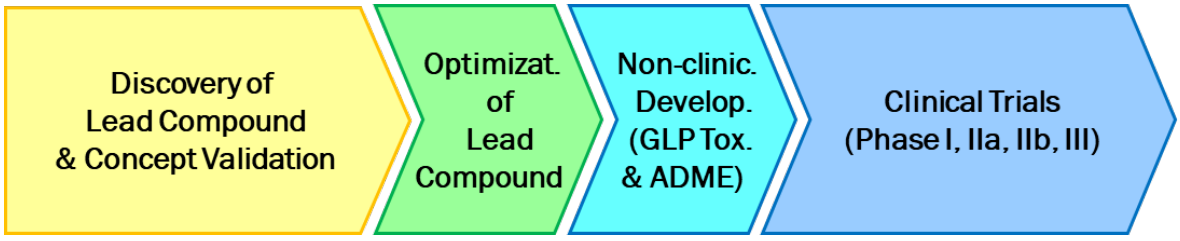


Fig. 1. Flow of research and development of drugs

clinical development, i.e., studies of selectivity, pharmacokinetics-pharmacodynamics, and early safety/toxicology.

It is very difficult for an academic institution like IIIS to conduct the non-clinical development due to large resources required for them. To fulfil the missing functions in the pharmaceutical science in IIIS

and complete the framework of sleep science, the collaboration with pharmaceutical companies is essential.

3-2. State of "bottom-up" undertakings from the center's researchers toward creating new interdisciplinary domains

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.

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, where all of IIIS member get together at the auditorium and introduce the research progress or published paper every week, 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 2018, we also resumed more informal meeting, i.e., Brie & Bordeaux (B&B) to help open communication and foster exchanges of ideas. One big lab or two smaller labs host B&B, organizing casual talks with snacks and drinks in the lounge of IIIS Building.

We hosted 17 WPI-IIIS Seminars in FY 2018, where we invited domestic and foreign researchers in sleep/neuroscience fields almost every other week. Consequently, 146 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.

As a result, the number of articles by collaborative research has drastically increased since FY 2015. The Nature papers published by Funato et al. in 2016 and 2018 are good examples of the successful internal collaborations involving 4 IIIS labs, in addition to multiple outside collaborators. Joining of early-career PIs, Honjoh, Abe, Hirano and K. Sakurai from outside, would accelerate generation of new collaborative research, and cross-sectional research activities are expected to further develop in the future.

3-3. Results of research in fused research fields

Describe the Center's record and results by interdisciplinary research activities yielded by the measures described in 4-1 and 4-2.

- In Appendix 1-2, list up to 10 of the Center's main papers on interdisciplinary research that substantiate the above record of results, and describe their content.

As described in Appendix 1-2, there are 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) morphine sedative effects, iv) PTSD and v) anxiety disorder, and vi) addiction to smoking, alcohol and psychotropic drugs.

In these studies, neuroscience labs were in charge of identifying molecular targets suitable for treatment of given diseases (indications), e.g., 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 its many derivatives. 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.

Even within basic biology, interdisciplinary research activities were crucial to achieve a breakthrough such as elucidating the mechanisms of sleep/wake regulation. An approach in molecular genetics, the forward genetics was powerful method to study a biological mechanism without any hypothesis. The collaboration between 2 groups studying molecular genetics and neuroscience let us discover and annotate genes involved in the sleep/wake regulation. The identification of genes, however, just gave us a clue to solve the question, and a powerful method of biochemistry/molecular cell biology, i.e., proteomics, gave an insight into molecular substrates of sleep need. The molecular basis of predator odor-evoked innate fear was also uncovered by the joint research between the molecular genetics and neuroscience.

Although we have not published yet, a few translational (TR) studies in which neuroscience/pharmacology labs and human sleep physiology labs have collaborated are under way. A good example of TR study is comparing effects of an orexin receptor antagonist and a GABAA agonist on human physical and cognitive functions. In animal studies, motor functions were impaired by GABAA agonists in a dose-dependent manner, while motor co-ordination was not affected by 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.

Another good example of TR studies, in which human sleep physiology labs are involved, is the development of a sleep measuring system for diagnosis. 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 a sleep measuring system, in which 3 groups, i.e., 1) IIIS, 2) Center for Computational Science, University of Tsukuba (CCS), and 3) Cyberdyne Inc., collaborate to develop an EEG-measuring-wearable device and algorithms/software based on the artificial intelligence for fully-automated sleep staging. CCS and Cyberdyne are responsible for development of the AI-based-software and the wearable device, respectively, while IIIS takes charge of their clinical tests/validation and the collection of the training data for AI programming.

In FY 2017, the team succeeded in developing the 1st prototypes of the wearable device developed by Cyberdyne Inc., with 3 channels of EEG and the AI-based-software for sleep staging of polysomnography (PSG) data. Based on this achievement, the spin-out of IIIS, S'UIMIN Inc. was established in October 2017 and succeeded in raising fund of ¥700 M in Capital from Mirai Creation Fund operated by SAPIX in November 2018. In March 2019, the development of the 2nd prototype of the wearable device was developed by NeuroSky Co., and the AI-based-software with improved performances was finished. The first pilot study on sleep using the wearable device is planned in FY 2019.

4. Realizing an International Research Environment (within 4 pages)

4-1. International Circulation of Best Brains

4-1-1. Center's record of attracting and retaining top-world researchers from abroad

Describe the participation of top-world researchers as PIs and their stays as joint researchers at the Center.

・ In Appendix 3-2, give the number of overseas researchers among all the Center's researchers, and the yearly transition in their numbers. In Appendix 4-2 give the achievements of overseas researchers staying at the center to substantiate this fact.

The overseas PIs have actively participated in the research activities at IIIS. While Liu and Greene have contributed to IIIS through their research activities in University of Texas Southwestern Medical Center (UTSW) as Satellite PIs, they have also established their own labs as PIs in the core group of IIIS since FY 2013 and engaged in lively research activity. Liu stayed at IIIS for 58 days during 6 visits to Japan in FY 2013, 98 days on 6 visits in FY 2014, 108 days on 7 visits in FY 2015, 129 days on 5 visits in FY 2016, 87 days on 5 visits in FY 2017. In FY 2018 he was appointed to the Investigator of National Institute of Biological Science, Beijing (NIBS) besides UTSW and IIIS, and the collaborative research agreement for the cross-appointment was executed among 3 institutions. In spite of the reduction of his efforts for IIIS, he stayed in IIIS for 65 days during 5 visits in FY 2018. On the other hand, Greene stayed at IIIS for 20 days on 2 visits to Japan in FY 2013, 17 days on 2 visits in FY 2014, 30 days on 3 visits in FY 2015, 28 days on 2 visits in FY 2016, 28 days on 3 visits in FY 2017 and 32 days on 3 visits in FY 2018. Both Greene and Liu actively contribute to the management of IIIS by participating in the PI meeting 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 7th WPI-IIIS Symposium held on December 20, 2018 at Tokyo Conference Center, 4 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 three of the foreign guests to IIIS to hold the post-symposium seminar to let researchers in Tsukuba community share the recent progresses in sleep research.

We hosted 17 WPI-IIIS Seminars in FY 2018, where we invited domestic and foreign researchers in sleep/neuroscience fields almost every other week; 8 speakers from overseas gave us lectures and the ratio of foreign researchers was 47% of the total seminar speakers in FY 2018. Consequently, 146 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 you can see in Appendix 4-2, 24 excellent researchers visited IIIS except for PIs and the speakers of IIIS Symposiums and IIIS Seminars. They all received a lecture from 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.

4-1-2. Employment of young researchers at the Center and their job placement after leaving the Center

Describe the Center's employment of young researchers, including postdoctoral researchers, and the positions they acquire after leaving the Center.

・ Enter the following to substantiate the facts provided above:
- In Appendix 4-3, describe the Center's state of international recruitment of postdoctoral researchers, the applications received, and selections made.
- In Appendix 3-2, give the percentage of postdoctoral researchers employed from abroad
- In Appendix 4-4, describe the positions that postdoctoral researchers acquire upon leaving the Center.

IIIS actively has engaged in international open recruitment by placing job advertisements on websites such as the homepage of IIIS, jREC-IN jobsite and naturejobs.com, etc. We renewed IIIS's Website completely in December 2017, and it became possible for foreign researchers to select and apply directly for the laboratory matching to their interests and expertise. Therefore, the number of applications for researchers in 2018 was reduced to 33 cases. The number of applicants in each year is as shown in Appendix 4-3.

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 2018, six foreign researchers (1 Chinese, 1 French, 1 Spanish, 1 Indian, 1 Nepalese, and 1 Korean) joined us including 4 through open international solicitations. Most of them stayed at IIIS to obtain skills and knowledge of sleep research, to advance their career paths.

Ex-IIIS young researchers acquired positions in Japanese top-level universities; promoted to a professor at Daiichi University of Pharmacy, appointed to assistant professors at University of Tokyo and, obtained a postdoc position in the University of Illinois Chicago, or employed as a postdoc in Massachusetts Institute of Technology after finishing Ph.D. at IIIS. Research achievements and experiences at IIIS contribute to the career development of many young researchers, and the number of the acquired positions outside IIIS has been increasing.

4-1-3. Overseas satellites and other cooperative organizations

- In Appendix 4-1, describe the state of cooperation with overseas satellites and other cooperative organizations. In Appendix 4-5, describe the state of the Center's agreements concluded with these organizations.

(1) Satellite institutions

University of Texas Southwestern Medical Center (UTSW)

As the Investigator of Howard Hughes Medical Institute (HHMI), Yanagisawa had served for UTSW for more than 20 years, which has nurtured a close relationship as the first IIIS Satellite since FY 2012. The four Satellite PIs (Joseph Takahashi, Robert Greene, Carla Green and Qinghua Liu) have conducted research collaboration under collaborative research agreement and/or sponsored research agreement since the WPI research funds are provided.

Under the joint appointment (35:65) between UTSW and University of Tsukuba, Liu serves as a Professor in IIIS to engage in studies of the intracellular signal transduction of neurons regulating sleep by phosphoproteome using mass spectrometric techniques, while he studies the molecular mechanism of innate fear by forward genetics using the ENU mutagenesis. His intellectual property rights should belong to both universities based on the joint appointment.

C. Green engages in the sponsored research into RNA analysis of sleep-deprived mice, and R. Greene covers the sponsored research on sleep homeostasis and the sleep-awakening control of adenosine. J. Takahashi conducts the sponsored research on circadian rhythm control of sleep.

National Institute of Biological Sciences (NIBS)

As described above, Liu had been jointly appointed between UTSW and University of Tsukuba. As of January 2019, however, he was appointed to the Investigator of NIBS and a new collaborative research agreement was executed for the cross-appointment among three organization, NIBS, UTSW, and University of Tsukuba. He serves as Investigator at NIBS, Associate Professor at UTSW and professor at IIIS with relative efforts of 55:25:20, respectively. His primary research commitment is to his lab at NIBS.

Other Satellites

In order to facilitate the communication and progress of the collaborations between IIIS and the satellite institutions, we have periodical internet-based video conferences. Also, these Satellite PIs and the Center Director regularly visit each other in person as Appendix 4-1. We also describe the state of the Center's agreements with the Satellites in Appendix 4-5.

(2) Partner institutions

We have started a collaboration with Sleep Disorder Centre, Neurology Department, Gui de Chauliac Hospital for the purpose to discover human genetic factors of sleep disorders using their biobank of sleep disorder patients. IIIS will perform exome and whole genome sequences of DNA extracted from the clinical samples from sleep disorder patients such as narcolepsy and idiopathic hypersomnia at Sleep Disorder Centre.

We have also started a joint research with Wenzhou Medical University to identify negative allosteric modulators of adenosine A_{2A} receptor ($A_{2A}R$). We will use the mA_{2A}R-CHO cells to screen low-molecular-weight compounds (synthesized at IIIS) for modulating effects on $A_{2A}R$ and Wenzhou Medical University send to IIIS a postdoctoral fellow with the experience in $A_{2A}R$ biology and neuroscience.

We also perform many collaborative research under material transfer agreement on animal models or compounds, and published many collaborative papers as Fig. 2 shows.

Fig. 2. Expanding Global Research Network

4-2. Center's record of holding international symposia, workshops, research meetings, training meetings and others

・ In Appendix 4-6, describe the main international research meetings held by the Center.

IIIS hosts International Symposium every year since the establishment in 2012. About 200 of researchers and students participate each time, and enjoy lectures by prominent sleep researchers from Japan and abroad and active scientific discussions. Many invited speakers disclose unpublished data of their studies, which inspire new ideas and expand collaboration opportunities.

Since 2014, we have co-hosted the annual symposia with other universities, research institutes and companies. The co-sponsored partners include RIKEN, The University of Tokyo, Wako Pure Chemical Industries, Ltd., MSD K. K., and the team of Grant-in-Aid for Scientific Research on Innovative Area, "Creation and Promotion of WILLDYNAMICS." The joint meetings attracted many participants, regardless of academia or industries, beyond the boundaries of the research fields and largely contributed to form novel networks. Particularly at the 7th Annual IIIS Symposium held in 2018, the number of participants from industries reached a record high of 50. It seems to reflect the growing visibility of IIIS and the social interest in sleep issues. In addition, the sponsorship also let us save the costs of holding the international meeting significantly.

We are planning to cohost the next annual symposium with "Ph.D. Program in Humanics," which was launched in November 2018 as one of the WISE Programs (Doctoral Program for World-leading Innovative & Smart Education) supported by MEXT, in order to boost interdisciplinary network and studies. In addition, it has been decided that the Center Director will be appointed to the Chairman of "The 45th Annual Meeting of Japanese Society of Sleep Research" in 2020 to be held in Yokohama, and it is expected that the domestic/international visibility of IIIS will be further boosted.

4-3. System for supporting the research activities of overseas researchers

Describe the Center's preparations to provide an environment conducive for overseas researchers to concentrate on their work, including for example living support in various languages or living support for their families.

University of Tsukuba has a department, "University of Tsukuba, 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 with JISTEC. 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 the 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 staffs on the campus of the university, in a highly convenient location and with well-organized support. Last year, the university established the Global Village, an international house and short-stay dormitory, to accept students and short-term trainees from overseas, which was shortly followed by the establishment of the on-campus Shopping Plaza, composed of a supermarket (KASUMI) and a cafe (Saza Coffee) for the purpose of improving 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 have charged with a wide range of work relating to budget planning, workforce 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.

Following the relocation to IIIS Building, 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.

Recently, we have introduced “Buddy System”, assigning a personal mentor, “Buddy” for newly arrived foreign researcher. Buddy shall be the first contact whenever they have questions or concerns in their daily lives such as shopping and showing the way around the campus, as well as lab activities such as basic rules/manners, handling of lab notebooks and so on.

4-4. Others

Describe the Center’s policy for sending Japanese researchers overseas to gain international experience, and give examples of how the Center is working to create career paths for its researchers within a global environment of researcher mobility.

IIIS encourages young researchers to get international experiences. IIIS instituted the Visiting Investigators System by itself for a postdoc who had to leave IIIS and go to London for 1 year due to her family matter in FY 2018. Because Grants-in Aid for Scientific Research (JSPS) are provided only to researchers who belong to Japanese research organizations, she was supposed to relinquish the grant. She, however, found a professor in a university in London who could accept her as a visiting fellow. We thus newly constituted the Visiting Investigator System to let her continue her study in London using the grant as IIIS Visiting Investigator. She has completed her project in London and is coming back to IIIS.

Additionally, in FY 2018 a researcher of IIIS participated in the Lindau Nobel Laureate Meetings, JSPS program, which was to foster highly talented Japanese researchers with a rich global view and experience for the future of Japanese academia. He received the “1st Prize: Best Presentation Award” at the meeting. He also acquired the JSPS Overseas Research Fellowship. This fellowship gave him an opportunity to carry out a long-term research abroad. He is now sent out to Massachusetts Institute of Technology as a postdoc.

University of Tsukuba aims to foster human resources with a global view by promoting international exchange to improve academic standards. In order to accomplish this goal, the university has established agreements with overseas universities and the United Nations University Institute of Advanced Studies, and offer a variety of activities such as delegating students and faculties abroad, transferring/exchanging credits with the universities and accepting faculties from abroad. In Graduate School of Comprehensive Human Sciences Majors of Medical Sciences, the partners for education and research exchanges include University of Edinburgh in England, University of Bordeaux (Bordeaux 2) in France, University of Bonn in Germany, National Taiwan University in Taiwan, and Vietnam National University, Ho Chi Minh City, in Vietnam.

IIIS encourages graduate students and young researchers to participate actively in the university’s programs as described above.

5. Making Organizational Reforms (within 3 pages)

5-1. Decision–making system in the center

Describe the strong leadership that the director is giving on the Center's operation and its effect, and the division of roles and authority between the Center and its host institution.
- In Appendix 3-3, draw a concrete diagram of the Center's management system.

Decision-making

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 expenditure are secured.

Principal Investigators' meeting (PI meeting)

Spearheaded by the administrative department, PI meetings were established to provide a periodic opportunity for PIs to openly discuss their opinions and concerns with the Center Director and to form consensus important matters concerning IIIS. In this meeting, the Director acts as the chairman and participants include all PIs and relevant staffs in the administration. PI meetings are held once a month with video conferencing capability to allow the Satellite PIs running their labs in the core group (Liu and Greene) to also attend. The functions of the steering committee (deliberation on institutional organization/management, research plans, etc.) of IIIS have also been attached to the meetings. Early-career PIs are also allowed to participate in the meetings, which gives a degree of motivation to the talented young researchers by granting them a forum for the management of their labs as independent researchers.

IIIS Personnel Committee

We established a personnel committee in IIIS to develop a system to appoint faculty members. The appointment system is different from the previous personnel system with less steps of the examination accelerated through intensive deliberations, i.e., 2 steps of the examination in total: IIIS Personnel Committee and Headquarters Personnel Council of the university. Our system let us determine and appoint IIIS faculties under the leadership of the Center Director. The committee has been held 23 times in total, and the appointment of 64 faculties and researchers (9 professors, 4 visiting professors, 11 associate professors, 1 visiting associate professor, 20 assistant professor, and 19 researchers) has been approved.

5-2. Arrangement of administrative support staff and effectiveness of support system

Describe the assignment of the Center's administrative support staff who have English language and other specialized skills, effort made in establishing the support system, and the system's effectiveness.

As in the previous fiscal year, IIIS Administration provided 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 (4 persons), the Accounting (3 persons), the Research strategy & Management (3 persons) and the Alliance & Communication (3 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, strived to resolve various problems that required coordination with the university headquarters.

The Research Strategy & Management Team was 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 year, the team received a URA who was assigned from the university headquarters to provide services of pre-awards and post-awards grant management.

The Alliance & Communication Team is led by a science communicator who has a good knowledge of outreach activities. She exercised active leadership in a range of activities, including the hosting of international symposiums and IIIS seminars, the preparation of press releases and the handling of the media, and successfully provided 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 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 percent of the administrative staff being bilingual and able to communicate smoothly with foreign researchers. Within IIIS, documents and papers are prepared in English or both in Japanese and English, in principle.

5-3. System reforms advanced by WPI program and their ripple effects

Concisely itemize the system reforms made to the Center's research operation and administrative organization, and describe their background and results. Describe the ripple effects that these reforms have on the host institution. (If any describe the ripple effects on other institutions.)

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 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/principal investigator for 20 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. 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.

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

From FY 2015 at the university, a quantitative evaluation index concerning research performance in terms of published papers and writings, granted external funding, and research alliance with public and for-profit organizations, was being established. We were thus considering the index as an evaluation tool to build a system of merit-based compensation. The salaries for the administrative staff members should be determined by the Center Director, based on the opinion of the Administrative Director.

Authority over personnel matters and simplification of the appointment system

As described before, IIIS Personnel Committee was established and distinctive authority over personnel matters was assigned. Only 3 research centers in the university, i.e., IIIS, TARA Center and the Center for Computational Sciences, 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.

Joint appointment system

With the purpose of enabling Yanagisawa to occupy concurrent posts at University of Tsukuba and UTSW, the joint appointment system was newly introduced to University of Tsukuba in March 2014. At the same time, a collaborative research agreement was concluded between University of Tsukuba and UTSW to determine terms and conditions of the research alliances accompanied with the joint appointment. In response to the execution of the agreement, University of Tsukuba made the tenure appointment of Yanagisawa as of April 1, 2014. Subsequently, Liu was also employed from FY 2014 under the joint appointment system, demonstrating, in the university, IIIS take the initiative in implementing the research alliance with overseas universities and offer model cases of the cross-appointment. Following to our cases, the number of the cross-appointment has been increasing rapidly and there are 35 cases in the university now.

Tsukuba Short-term Study Program (TSSP)

As for the short-term stay for training we have already accepted many trainees as described in Appendix 5-1. The system we have used to accept the trainees was the workshop type of Tsukuba Short-term Study Program (TSSP) of the university, which allows even short-term trainees to use the student dormitory at a nominal fee and requires no entrance and tuition fees. However, the term of the program was limited to less than 3 months. We were requested to accept undergraduate students as interns for the periods longer than 3 months by a few professors in China and Vietnam, and we thus consulted the Vice President in charge of student affairs for a solution. The student affairs division of the university reviewed the system and regulations, whereupon the bylaw for TSSP was revised in March 2016 and the stay for training within a year became possible.

5-4. Support by Host Institution

The following two items concern the support that the host institution provides the Center. Describe the functional measures that the host institution has taken to sustain and advance the Center's project. That include those items of support that it committed to at the time of the initial project proposal submittal or in its revised commitment following the project's interim evaluation.

5-4-1. Record of host institution support and its effects

- In Appendix 6-1, describe the concrete measures being taken by the host institution.

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 supported ¥1.8 B for the costs of IIIS Building, facilities, equipment, exterior, landscaping including a parking lot and moving from temporary labs distributed among 4 places in the university campus.
4. The university supports most of the personnel cost of Vice Center Director, Sakurai.
5. The university delegates 3 university personnel to the administrative positions, including Vice-Administrative Director, in the key areas of general affairs and accounting. Since July, 2015, a URA has been also assigned to the Research Strategy and Management Team.
6. IIIS rents for ¥70 M/year a part of the new research building (2,000 m^2) that was expanded by the university funds, while the University bore more than ¥84 M of utility costs of IIIS Building.
7. From April 2019, the university supports the research spaces at Innovation Medical Research Institute to expand IIIS activity especially for the Human Sleep Lab.

5-4-2. Position of the Center within the host institution's mid-term plan

- To Appendix 6-2, excerpt the places in the host institution's "Mid-term objectives" and/or "Mid-term plan" that clearly show the positioning of the WPI center within its organization.

During the third mid-term plan of University of Tsukuba starting from FY 2016, the university aims to develop a globally unrivaled frontier research of 2 objectives, i.e., research for the quest for truth and research for innovation contributing to society, in wide-ranging disciplines and research fields. To realize these objectives, the university is making a plan of reorganization/restructuring/merger of all research centers and will implement it during the period of the 3rd mid-term plan. IIIS is positioned as a pioneering model of the forefront research organization the mid-term plan targets.

5-5. Others

Describe efforts advanced to foster young researchers (e.g., start-up funding, autonomous research environment) and to enlist female researchers.

- In Appendix 3-1, 3-2, give the transition in the number and ratio of female researchers.

Start-up Funding

Research start-up funds were offered to PIs invited from outside of University of Tsukuba. The provision of these research funds were planned by the Administrative Director and carried out based on the budget plan decided by the Center Director.

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.

6. Others

In addition to the above 1.-5. evaluation items, note any of the Center's leading activities, distinctive features or other important points that denote its status as an "internationally visible research center."

6-1. Unique outreach activities

As it was mentioned in 2-6-2, we conducted a crowdfunding project in FY 2018 and successfully raised fund of ¥3,566,000. In addition to public relations activities, the Alliance & Communication team organized the internal events to encourage open communication and collaborations among labs.

Crowdfunding

From March 14 to May 31 2018, we launched the crowdfunding for the purpose of improving publicity and acquiring research budgets for a large-scale survey of the relationship between sleep and mental health. It was the very first crowdfunding project for the WPI research centers, and was widely covered by various media such as the Asahi Shimbun, the Yomiuri Shimbun and the Mainichi Shimbun. However, the amount of donations reached only 50% at the end of April. We thus conducted “Nico-Nico” broadcast for 36 hours to boost donations. We broadcasted live sleeping humans, mice, and nematodes with fixed cameras, and introduced our research results by researchers and graduate students of IIIS, including Yanagisawa and Sakurai. In the program, we also conducted IIIS lab tour so that people could see the inside of IIIS labs, which usually they could not get in. The total number of viewers was 115,926 and more than 95% answered that it was good or great in the questionnaire. This program contributed to the crowdfunding, and we successfully reached the target amount of ¥3,000,000 (total: ¥3,566,000) and made publicity for our institute and researches especially among the young generation.

As thank you gifts, we offered the sleep analysis using an actigraph and a sleep diary, provided that donors agreed to participate in our epidemiological sleep study. We made a personal report to each donor based on the result of the sleep analysis so that people could reconsider their own lifestyle and sleep habit. We also gave, to the donors who made a large contribution, lectures by IIIS researchers, opportunities of discussion with IIIS researchers, IIIS lab tour, etc.

Our new attempt attracted the attention of media and was reported in a news program "Keyaki Hills" in Abema TV, an internet broadcast, on September 12, 2018. We found that broadcasting through the internet could be a new strategy of outreach.

Events for IIIS members

We have conducted the internal events in order to encourage the open communication and exchange of ideas possibly leading to collaborations among labs. As described in 3-2, we have held Brie & Bordeaux (B&B) 20 times so far. It is a casual meeting with nice drinks and foods, and people enjoy short research presentations and discussions. We also plan to hold “IIIS Retreat,” another casual meet-up event for IIIS members, in FY 2019. We nominated a graduate student for the chairman of a planning committee, and he has organized the committee with students representing all labs. We hope it could enhance the communication among students studying in IIIS and give them an opportunity to gain the valuable experience.

6-2. Further facility development

R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI) supported by Toyota Motor Corporation has moved into the south side on 4th floor of IIIS Building. We are planning a long-term collaboration with them and, as the first step, we are developing the Mobile Sleep Lab based on a fuel cell bus lent by Toyota at no charge, taking advantage of its characteristics; the fuel cell bus can supply bulk power for air conditioning and sleep measurement without noise and vibration, and access easily to subjects at living/working environment.

Another exciting collaboration project with the School of Art in the university, called “Art Street-Satellite Gallery” for which we provide several spaces in IIIS Building to exhibit a part of the collection of prize-winning artworks created by the students of the School of Art, and four artworks have newly been displayed. In addition, Ms. Atsuko Tsurumi, an artist who continues to present “dreams” throughout her life, donated four paintings and they are also displayed on the wall of the building.

6-3. Enhancing research ethics

To avoid research misconduct, we have launched educational campaigns for research ethics since FY 2015 and we held 5 seminars in the series of Research Ethics Seminar as follows;

1. The first seminar entitled “Research ethics and risk management: Lessons learnt from the STAP incident” by Ms. Momoko Suda on September 29, 2015.
2. The second seminar entitled “Research Misconduct: The Beginning of the End What Makes a Scientist ’Dr. Con Artist’?” by Dr. Susumu Inamoto on October 4, 2016.

3. The third seminar entitled “Research misconduct - lessons learnt from case studies” by Dr. Toshio Kuroki on March 22, 2017.
4. The 4th seminar entitled “Professional ethics for scientists and journalist” by Mr. Takao Fujiyoshi on September 25, 2017.
5. The 5th seminar entitled “Anti-Vax Campaign Using Pseudoscience and Lawsuits” by Dr. Riko Muranaka on February 13, 2018.

In addition, we introduced the official laboratory notebook of IIIS to formalize and let everyone use a common hard-covered laboratory notebook for better data management and prevention of research misconduct. We prepared the standard operating procedures (SOP) on purchasing, distribution, weekly check by mentors, storage, return, archiving, etc. One important key issue on SOP is that the laboratory notebook shall be kept under the supervision of the responsible PI. The responsible PI or a faculty member/postdoc appointed by the responsible PI, shall periodically (once a week is suggested) check the laboratory notebook.

6-4. Ph.D. Program in Humanics

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. The WISE Program is designed to support each university’s initiative to establish a 5-year doctoral degree program with a concentration of the world’s best educational and research capabilities. The WISE Program encourages applicant universities to build on their own strengths and capitalize on their graduate school reform outcomes, while engaging in organizational cooperation with universities, research institutions, private-sector companies and other entities in and out of Japan. In FY 2018, which was the first year of the WISE Program, 54 applications were filed, and 15 projects, including our Ph.D. Program in Humanics, were 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.

Enabling the sustainable development of this degree program requires acquisition of financial resources after the WISE Program that finishes in only 7 years. We are therefore preparing to set up the Collaboration Council as a portal for academic-industrial alliance. This is expected to produce partnerships with companies in a wider range of sectors than those IIIS alone had made before.

The WISE Program’s budget will allow us to employ 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.

7. Center's Response to Results of FY 2018 Follow-up (including Site Visit Results)

* Describe the Center's response to results of FY 2018 follow-up. Note: If you have already provided this information, please indicate where in the report.

7-1. Center's Response to Site Visit Report

(1) *Although each project is going well, there still appears to be some distance between the projects, such as between forward genetics and neural circuits or forward genetics and medical chemistry.*

(2) *To strengthen the integrated sleep science, strategies for the next steps are required.*
We would like to know what the next steps and goals are after identifying the sleep controlling circuits by optogenetic and pharmacogenetic methods. For an example, to move beyond the simple circuits so far identified, systems neuroscience will be important to develop more integrated views.

As described in the Progress Plan, new discoveries in forward genetics that the identified genes encode molecules involved in the intracellular signal transduction such as Sik3 raise new questions. It is a new challenge how to elucidate the regulation of sleep/wakefulness by integrating the neural circuits switching sleep and wakefulness in time periods of a second or less, with the intracellular signal transduction pertaining to sleepiness or sleep need, which require minutes to hours to take place. It has become clear that more than ten years of research will be required to perform comprehensive analyses and identification of neural circuits responsible for the regulation of sleep/wakefulness, and further to integrate our understanding of neural circuits with that of intracellular signal transduction.

We are thus proposing the new strategy to concentrate all the resources to be provided by the WPI program for the next five years (from FY 2022 to FY 2026) on neuroscience and human molecular genetics to solve the mystery of sleep.

The elucidation of the mechanism regulating sleep/wakefulness, through integrated understanding of the neural circuits with intracellular signal transduction, would let us identify good molecular targets for drugs. Since the first step in drug discovery is the identification of good molecular targets, the integrated understanding will bridge between the forward genetics and medicinal chemistry.

(3) *Certain biochemical and cell biological approaches will be necessary after the genetic approaches. For an example, spatial and temporal monitoring of Sik3 activity is important for better understanding the roles of Sik3 in sleep control. Identifying Sik3 substrates is also important.*

To visualize SIK3 activity in vivo and in real-time, we have collaborated with Dr. Michiyuki Matsuda, Kyoto University, to develop FRET and BRET probes. We have already made transgenic mice expressing these probes. We are also ready to use a caged compound to see effects of acute inhibition of Sik3 on sleep/wakefulness. To identify Sik3 substrates, we are conducting several approaches as follows. The first approach is a biochemical study to see effects of the combination of a SIK3 inhibitor and phosphatase inhibitors, which should be followed by LC/MS-MS analysis. The second approach is a study of the substrate candidates. Since there are several papers reporting SIK3 substrates, we are conducting several biochemical and molecular biological experiments to examine roles of the substrate candidates in the sleep regulation. The third approach is a genetic study. We are running a suppressor screening of SIK3 mutant mice, which may lead to identification of upstream and downstream molecules.

(4) *Activities with IIIS's domestic satellites are not visible.*

IIIS continues and strengthens the collaboration with domestic satellites as follows;

1) We collaborated with Shimizu and Kanbayashi, Akita University Graduate School of Medicine, in the study of the orexin agonist, and they were co-authors of the PNAS paper on the narcolepsy therapy published by Kaushik, Yanagisawa et al. in 2018. Shimizu, however, retired from Akita University as of March 31, 2018. We thus asked his successor, Mishima, who used to be the director of Sleep Center at National Center of Neurology and Psychiatry (NCNP) in Tokyo, to take over the Satellite PI position. We have already executed the research collaboration agreement to continue the collaboration with Akita University with a wider scope covering not only narcolepsy but also insomnia diagnosis and cognitive behavior therapy.
2) We have recruited Kanbayashi, former associate professor at Akita University, to join IIIS as of April 1, 2019. He will be jointly appointed to PI in IIIS and Director at Ibaraki Prefectural Medical Center for Psychiatry by University of Tsukuba and Ibaraki Prefecture, respectively. Since he will conduct

clinical research at the Medical Center, it will be regarded as another domestic satellite.

(5) *As an outreach activity, organizing a regional competition for Brain Bee would be fruitful both for making the institute better known to the local people and for putting local high school students in contact with neuroscientists at a young age.*

We decided not to hold regional competition for Brain Bee because:

1) Since RIKEN BSI has already been the organizer of the competition, it seemed that the merit of IIIS becoming a new venue in Japan would be limited.
2) In addition, as mentioned in 2-6-2, we have already accepted a lot of visitors from junior/senior high schools and offered various learning programs. These programs have become good opportunities for students to get familiar with the latest neurosciences.

(6) *Although the unit for human sleep research is unique and attractive, its aims are a bit diverse and its relations to other units unclear. Interdisciplinary research projects between experimental medicine and basic biology and those between experimental medicine and pharmaceutical science have to be accelerated to promote their translational potential and to obtain funding for sustaining the organization.*

In accordance with one of our research objectives, the strategies of our studies of experimental medicine are as follows.

1) Study new remedies introduced to markets recently, e.g., the orexin antagonist, functional mattresses, supplements, functional foods, etc.
2) Develop the automated sleep measuring system for home use (a new diagnosis) in collaboration with S'UIMIN Inc.
3) Conduct cohort and intervention studies by using the automated sleep measuring system in collaboration with F-MIRAI.
4) Study novel remedies created in collaboration with industries including drugs, devices, and software of cognitive behavior therapy.

Expansion of the experimental medicine in IIIS had been a pending issue, and we thus newly established a facility for human sleep studies, Human Sleep Lab in Innovation Medical Research Institute located in the Kasuga Campus, University of Tsukuba as of March 31, 2019. This 211 m^2 wide facility near Tsukuba Station has 4 beds of sleep measuring chambers, a bath room, and 1 bed of human calorimeter chamber (for whole room indirect calorimetry during sleep), which was moved from IIIS Building. It allows the sleep measurement of multiple subjects (up to 5) in parallel and improves efficiency of our human sleep research significantly. We also reinforce the group of experimental medicine by recruiting the new PI, Kanbayashi, as mentioned above.

7-2. Center's Response to FY 2018 Follow-up

(1) *To strengthen the integrated sleep science, strategies for the next steps are required. We would like to know what the next steps and goals are after identifying the sleep controlling circuits by optogenetic and pharmacogenetic methods.*

As described in the Progress Plan, new discoveries in forward genetics that the identified genes encode molecules involved in the intracellular signal transduction such as Sik3 raise new questions. It would be a new challenge how to elucidate the regulation of sleep/wakefulness by integrating the neural circuits switching sleep and wakefulness in time periods of a second or less, with the intracellular signal transduction pertaining to sleepiness or sleep need, which require minutes to hours to take place. It has become clear that more than ten years of research will be required to perform comprehensive analysis and identification of neural circuits responsible for the regulation of sleep/wakefulness, and further to integrate our understanding of neural circuits with that of intracellular signal transduction.

Verification of the integrated understanding between the neural circuits and the intracellular signal transduction in humans would be another challenge we take up in the next step. We will carry out large-scale whole genome sequencing for a large number of individuals with extreme phenotypes and perform big data analysis to identify/validate genes responsible for the phenotypes.

We are thus proposing the new strategy to concentrate all the resources to be provided by the WPI program for the next five years (from FY 2022 to FY 2026) on neuroscience and human molecular

genetics to solve the mystery of sleep.

(2) *Certain biochemical and cell biological approaches will be necessary after the genetic approaches. For an example, spatial and temporal monitoring of Sik3 activity is important for better understanding the roles of Sik3 in sleep control. Identifying Sik3 substrates is also important.*

To visualize SIK3 activity in vivo and in real-time, we have collaborated with Dr. Michiyuki Matsuda, Kyoto University, to develop FRET and BRET probes. We have already made transgenic mice expressing these probes. We are also ready to use a caged compound to see effects of acute inhibition of Sik3 on sleep/wakefulness. To identify Sik3 substrates, we are conducting several approaches as follows. The first approach is a biochemical study to see effects of the combination of a SIK3 inhibitor and phosphatase inhibitors, which should be followed by LC/MS-MS analysis. The second approach is a study of the substrate candidates. Since there are several papers reporting SIK3 substrates, we are conducting several biochemical and molecular biological experiments to examine roles of the substrate candidates in the sleep regulation. The third approach is a genetic study. We are running a suppressor screening of SIK3 mutant mice, which may lead to identification of upstream and downstream molecules.

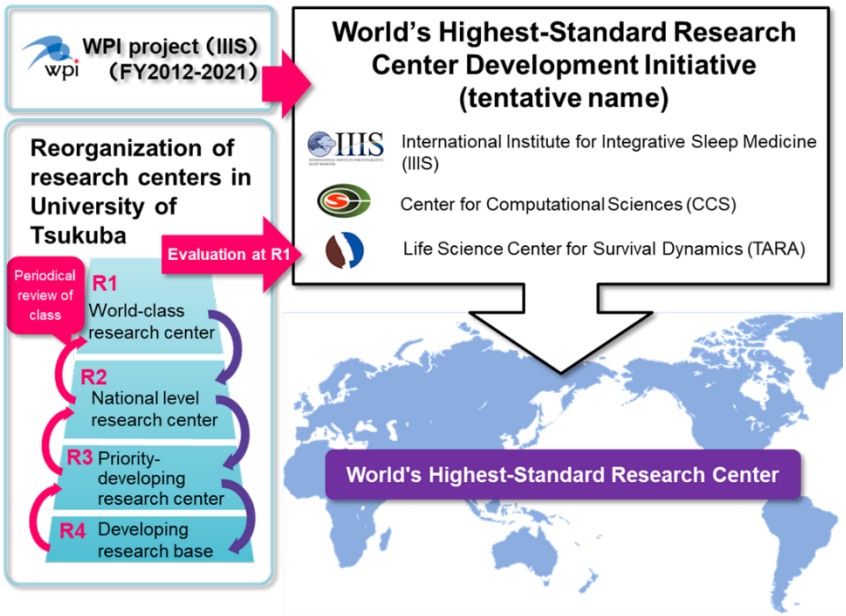
(3) *The next few years will be crucial for establishing IIIS as a sustainable institute. Ongoing effort to achieve this should be continued with tight collaboration with University of Tsukuba's top management.*

To make the foundation of IIIS sustainable, the President of University of Tsukuba has repeatedly stated at the WPI Program Committee that PIs with a proven track record of achievement should receive the status of "tenure." Yanagisawa and T. Sakurai have already acquired this status, and in FY 2018, with the cooperation of the Faculty of Medicine, a female PI (Hirano) was appointed to a tenure track assistant professor by using the strategic position secured by the university.

Based on the objective evaluation, the Center Director nominates PIs that are qualified for tenure (or tenure review in future). To grant tenure to these PIs, the university will secure positions and funds by 1) requesting a quota for new faculties needed to establish Cross-border Research Center Developing Initiative and 2) strategic reallocation of internal resources through restructuring/reorganizing the research centers. In fact, we were able to secure funds necessary to grant tenure to one PI, Associate Professor Hayashi, and non-PI Associate Professor Kutsumura, who has been appointed to succeed Professor Nagase. As a result, five PIs, including Kutsumura, have been tenured so far. In the future, with the aim of expanding Cross-border Research Center Developing Initiative, we will continue to secure positions and funds to provide all the PIs listed in Appendix 1 with the opportunity of tenure review within four years.

(4) *Expected, but impressive, progress is seen not only in science but also in system reforms. The spirit of IIIS is to be extended to entire University of Tsukuba's administration, research, and education.*

University of Tsukuba aims at sharing the initiatives that IIIS has worked on, including the promotion of advanced and interdisciplinary researches as well as internationalization and system reforms, with other world-class research centers (Center for Computational Science and TARA), and is working to establish "Cross-border Research Center Developing Initiative" (tentative name). By sharing research strategies and knowledge/experiences in organizational management, intellectual property rights/alliance strategies, we could establish new research management to lay the groundwork for world-class research centers that can later be applied to the rest of the university.



(5) *Collaboration with Toyota will help to make the institute sustainable, but we wonder if this collaboration makes the institute research to be more applied one.*

We are planning to collaborate with Toyota in following two steps;

1) In the first step from FY 2018 to FY 2021, we collaborate with R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI), which is the joint project between Toyota Motor Corporation and University of Tsukuba starting from April 2017 to develop fundamental technologies for regional communities to realize Society 5.0, to develop social measurements by applying Internet of Things (IoT), and to resolve the social engineering issues through the big data analysis by artificial intelligence. F-MIRAI moved into the future expansion space in IIIS Building in FY 2018. We started actual collaboration from October, 2018 to develop a wearable sleep measurement device in the collaboration with S'UIMIN Inc. We are also developing the Mobile Sleep Lab based on a fuel cell bus lent by Toyota at no charge, and will perform translational research by taking advantage of its characteristics.
2) For the second step from FY 2022 to FY 2031, we strive to get a grant comparable to the WPI subsidy (¥600 M/year for 10 years) from Toyota Mobility Foundation. According to Dr. Takahara, the large grant from the Foundation has no restrictions on use, and there would be no concerns limiting the studies of neuroscience and human molecular genetics. It would definitely contribute to the sustained operation of IIIS after the WPI program funding ends (even without 5 year extension), but the competition would be very keen.

(6) *It is important not to over-estimate the funding that can come in from S'UIMIN or other licensing revenues. University-wide licensing revenue typically only accounts for less than 3 or 4% of major university budgets in the U.S., which has a well-developed system.*

We agree not to over-estimate the funding from S'UIMIN or other licensing revenues. Even if S'UIMIN succeeded in launching the sleep measurement services or licensing the orexin receptor 2 agonist to a pharmaceutical company as a private TLO, it would take 5 to 10 years to gain royalties sufficient for IIIS operation.

Therefore, we have also directed our efforts to increase external funds. As a result, total amount of the funds executed each year by the researchers in IIIS core team have drastically increased as ¥1.5 M in FY 2012, ¥63.8 M in FY 2013, ¥178 M in FY 2014, ¥282 M in FY 2015, ¥611 M in FY 2016 and ¥667 M in FY 2017. In FY 2018, it reached ¥770 M, 133% of the WPI subsidy in FY 2018. We continue our efforts to secure external funding in an amount greater than that of the WPI subsidy.

For the years after the end of the WPI grants support period (after FY 2022), we strive to acquire a large-scale funding by:

1) pursuing the possibility of alliance projects with the Toyota Mobility Foundation, and
2) applying for Japan Science and Technology Agency (JST)'s Future Society Creation Program, the Cabinet Office's Moonshot Research and Development Initiative, etc.

Appendix 1-1 List of Papers Underscoring Each Research Achievement

* List papers underscoring each research achievement [1] ~ [15] listed in the item 2-1 "Research results to date" of 2. "Advancing Research of the Highest Global Level" (up to 30 papers) and provide a description of the significance of each (within 10 lines).
* For each, write the author name(s); year of publication; journal name, volume, page(s), and article title. Any listing order may be used as long as format is the same. If a paper has many authors, underline those affiliated with the Center.
* If a paper has many authors (say, more than 10), all of their names do not need to be listed.
* Place an asterisk (*) in front of those results that could only have been achieved by a WPI center.

*[1] **Opening the black box of sleep homeostasis through large-scale forward genetics and phosphoproteomics**

*1. Wang ZQ, Ma J, Miyoshi C, Lie YX, Sato M, Ogawa Y, Lou TT, Ma CY, Gao X, Lee C, Fujiyama T, Yang XJ, Zhou S, Hotta-Hirashima N, Klewe-Nebenius D, Ikkyu A, Kakizaki M, Kanno S, Cao LQ, Takahashi S, Peng JM, Yu YH, Funato H, Yanagisawa M, Liu QH (2018) Quantitative phosphoproteomic analysis of the molecular substrates of sleep need. *Nature.* **558** (7710):435-439.

Sleepiness, or sleep need, gradually accumulates during wakefulness, and dissipates during sleep, thus ensuring sleep homeostasis. The neurobiological substrate of homeostatic sleep need is entirely unknown. Traditionally, in order to solve this puzzle, researchers have compared brains from sleep-deprived, very sleepy animals with brains from freely slept, not so sleepy animals. However, these tactics were unable to distinguish the true effect of increased sleep need from the influence of stress associated with sleep deprivation and from the effect of the wakeful state itself. In this study, we systematically cross-compared the whole-brain phosphoproteomic states of our newly discovered Sleepy mutant mice (with increased sleep amount and increased sleep need) and sleep-deprived mice (with decreased sleep amount and increased sleep need). We found that the cumulative levels of phosphorylation in a specific subset of mostly synaptic proteins gradually increase when sleep need accumulates, and their hyper-phosphorylated state is reversed when sleep need dissipates. Moreover, pharmacologically inhibiting Sik3 kinase in the brain decrease the incex of sleep need both in Sleepy mutant mice and sleep-deprived normal mice. The cumulative phosphostate changes in these proteins may underlie both sleep homeostasis and synaptic homeostasis.

*2. Honda T, Fujiyama T, Miyoshi C, Ikkyu A, Hotta-Hirashima N, Kanno S, Mizuno S, Sugiyama F, Takahashi S, Funato H, Yanagisawa M (2018) A single phosphorylation site of SIK3 regulates daily sleep amounts and sleep need in mice *Proc Natl Acad Sci USA.* **115**(41):10458-10463.

The neural substrate for sleep need, the basis for the molecular mechanisms determining daily sleep amounts, remain mysterious. In this study, we found that a single amino acid, Ser551, of the protein kinase SIK3 has a crucial role in the regulation of sleep need and daily non-REM sleep amounts. Importantly, S551 in SIK3 is evolutionally conserved as a site for PKA-driven phosphorylation from nematodes and fruit flies to mice and humans. This further implicates SIK3 in the molecular basis of homeostatic sleep/wake regulation.

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

New circuit-level experimental methods such as opto-/chemo-genetics and real-time neuronal imaging have led to increasingly detailed understanding of the executive neural circuitry that switches the brain between sleep and wake states. However, essentially nothing is known as to how "sleepiness," or sleep need, gradually accumulates during wakefulness and eventually drives the sleep/wake switch. In this tour-de-force study, we conducted a large-scale forward genetic screen of randomly mutagenized mice with EEG/EMG-based sleep/wake assessments. In this non-hypothesis-based, unbiased approach, we screened more than 8,000 mice and identified: i) a splicing mutation in the Sik3 protein kinase gene (Sleepy mutation) causing a marked increase in non-REM sleep amounts associated with a constitutively increased level of sleep need; and ii) a gain-of-function mutation in the Nalcn cation channel gene (Dreamless mutation) that

causes a significant decrease in REM sleep amounts. This study opened up an entirely new avenue of research tackling the fundamental mysteries of sleep regulation.

*[2] **The functions of REM sleep revealed from chemogenetic approaches**

*4. McEown K, Takata Y, Cherasse Y, Nagata N, Aritake K, Lazarus M (2016) Chemogenetic inhibition of the medial prefrontal cortex reverses the effects of REM sleep loss on sucrose consumption. *eLife.* **5**:e20269.

Insufficient sleep leads to increased consumption of weight-promoting foods. Especially, the amount of REM sleep has been associated with fat consumption in humans. To pursuit the role of REM sleep in food preference and address the underlying mechanism, the authors focused on mice. Putting mice on a wire-mesh-grid device was known to reduce REM sleep. Thus, the authors utilized this device. In this model of REM sleep reduction, the authors confirmed that mice consume more highly-palatable food, namely high-sucrose or high-fat diet. The authors further found that, when a brain area termed the medial prefrontal cortex (mPFC) was inhibited through chemogenetics, some of the effects of wire-mesh-grid device on consumption of highly-palatable food was reversed. Thus, REM sleep might affect food preference via the regulation of the (mPFC).

*5. Hayashi Y, Kashiwagi M, Yasuda K, Ando R, Kanuka M, Sakai K, Itohara S (2015) Cells of a common developmental origin regulate REM/non-REM sleep and wakefulness in mice. *Science.* **350**:957-961.

To elucidate the function of REM sleep, authors first identified neuronal cells that strongly regulate REM sleep. These neurons were located in the brainstem. Next, they established transgenic mice in which the neuronal activity of these cells could be artificially manipulated through chemogenetics. As a result, in this transgenic mouse, REM sleep could be either suppressed or increased at a desired timing. Interestingly, when REM sleep was inhibited, slow wave activity, a brain activity important for learning and memory, became gradually attenuated. Oppositely, when REM sleep was increased, slow wave activity was enhanced. Thus, REM sleep is crucial for the brain to generate slow wave activity. Based on this study, REM sleep is expected to contribute to memory formation and brain maturation via promoting slow wave activity.

*[3] **Deciphering Neuronal Circuits linking the Limbic System, Hypothalamus, and Brain Stem.**

*6. Saito YC, Maejima T, Nishitani M, Hasegawa E, Yanagawa Y, Mieda M, Sakurai T (2018) Monoamines Inhibit GABAergic Neurons in Ventrolateral Preoptic Area That Make Direct Synaptic Connections to Hypothalamic Arousal Neurons. *J Neurosci.* **38**(28):6366-6378.

During a search for neurons that make direct synaptic contact with histidine decarboxylase-positive (HDC+), histaminergic neurons (HDC neurons) in the TMN and orexin neurons in the LHA of male mice, we found that these neurons are heavily innervated by GABAergic neurons in the preoptic area including the VLPO. We further characterized GABAergic neurons electrophysiologically in the VLPO ($GABA^{VLPO}$ neurons) that make direct synaptic contact with these hypothalamic arousal-related neurons. These neurons ($GABA^{VLPO\rightarrow HDC}$ or $GABA^{VLPO\rightarrow orexin}$neurons) were both potently inhibited by noradrenaline and serotonin, showing typical electrophysiological characteristics of sleep-promoting neurons in the VLPO. This work provides direct evidence of monosynaptic connectivity between $GABA^{VLPO}$ neurons and hypothalamic arousal neurons and identifies the effects of monoamines on these neuronal pathways.

*7. Kodani S, Soya S, Sakurai T (2017) Excitation of GABAergic Neurons in the Bed Nucleus of the Stria Terminalis Triggers Immediate Transition from Non-Rapid Eye Movement Sleep to Wakefulness in Mice. *J Neurosci.* **37**(30): 7164-7176.

To determine whether the extended amygdala plays a role in sleep–wakefulness regulation, we examined the effects of optogenetic and pharmacogenetic excitation of GABAergic neurons in the bed nucleus of the

stria terminalis ($GABA^{BNST}$ neurons). Acute optogenetic excitation of these cells during NREM sleep resulted in an immediate state transition to wakefulness, whereas stimulation during REM sleep showed no effect. A dual orexin receptor antagonist, DORA-22, did not affect the optogenetic transition from NREM sleep to wakefulness. Chemogenetic excitation of $GABA^{BNST}$ neurons evoked a sustained wakefulness state, but this arousal effect was markedly attenuated by DORA-22. These observations suggest that $GABA^{BNST}$ neurons play an important role in transition from NREM sleep to wakefulness without the function of orexin neurons, but prolonged excitation of these cells mobilizes the orexin system to sustain wakefulness.

*[4] **The brain mechanism underlying the desire to sleep in boring situations**

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

By using chemo-genetic and optical techniques to remotely control the activities of adenosine A_{2A} receptors ($A_{2A}R$)-expressing nucleus accumbens (NAc) neurons and the behaviors they mediate, the Lazarus/Oishi lab discovered that nucleus accumbens neurons have an extremely strong ability to induce sleep that is indistinguishable from the major component of natural sleep, known as slow-wave sleep, as it is characterized by slow and high-voltage brain waves. Homoeostatic sleep pressure produced by sleep deprivation did not change the neuronal activity of NAc $A_{2A}R$ neurons, whereas motivational stimuli attenuated the activity of these neurons and reduced sleep amount. The paper revealed a sleep-inducing role of the NAc that is regulated by motivational factors.

[5] **Elucidation of the functions of thalamic matrix cells in regulation of cortical activity and arousal**

9. Honjoh S, Sasai S, Schiereck SS, Nagai H, Tononi G, Cirelli C (2018) Regulation of cortical activity and arousal by the matrix cells of the ventromedial thalamic nucleus. *Nat Commun*. **9**:2100.

To study roles of thalamus in the wake/sleep regulation, we focused on thalamic neural subpopulations. Thalamic neurons are largely divided into two subpopulations, “core cells” and “matrix cells”, based on their connectivity patterns. Core cells receive sensory information and project to a specific primary sensory cortex, whereas matrix cells project to widespread cortical areas nonspecifically. We showed that the activities of both core and matrix cells are high in wake and low in NREM sleep. We demonstrated that optogenetic stimulation of matrix cells caused global EEG activation and rapidly awoke all mice from NREM sleep. In contrast, optogenetic stimulation of core cells lead to cortical activation only locally and transiently, and never promoted behavioral arousal. Collectively, our data revealed specific roles of matrix cells in the global cortical activation and behavioral arousal.

[6] **Advanced our understanding of the biological clock regulating sleep/wake rhythms at cellular and molecular levels**

10. Hirano A, Pei-Ken Hsu, Zhang L, Xing L, McMahon T, Yamazaki M, Ptáček L, Fu Y (2018) Human DEC2 modulates orexin expression and regulates sleep duration. *Proc Natl Acad Sci USA.* **115**(13):3434-3439. doi:10.1073/pnas.1801693115.

Orexin is a quite important molecule regulating sleep/wake behavior and potentially useful for therapeutic application, while the regulatory system of its expression has been elusive. It was previously reported that a mutation in a transcription repressor, *hDEC2*, is highly associated with short sleep phenotype in humans. In this study, we addressed the mechanism of the sleep phenotype using a mouse model carrying the mutation. We demonstrated DEC2 binds to promoter region of orexin precursor gene in mouse brain and downregulates expression of Orexin. The human mutation alters the interaction of DEC2 proteins with transcription factors

cooperating with DEC2, resulting in abnormal expression of orexin. This study showed the regulatory mechanism of orexin expression and how sleep duration is determined in mammals.

11. Hayasaka N, Hirano A, Miyoshi Y, Tokuda IT, Yoshitane H, Matsuda J, Fukada Y (2017) Salt-inducible kinase 3 regulates circadian clocks in mice by destabilizing PER2 protein. *eLife*. **6**:e24779.

We previously identified *Sik3* as a sleep regulating gene (Funato et al., Nature, 2016), although other functions of *Sik3* in the central nervous system have been totally unknown. In the present study, we demonstrated SIK3 is a key component in the circadian clock system. *Sik3* knockout mice exhibited abnormal behavioral rhythms and cellular rhythms. We also identified PER2, one of core clock proteins, as a substrate of SIK3. SIK3 kinase activity is required for degradation of PER2 in cell culture. Importantly, PER2 degradation triggered by SIK3 is independent of casein kinase, which has been well known to promote PER2 degradation and regulate the circadian period, suggesting that SIK3-mediated phosphorylation is a novel regulatory mechanism of PER2 turnover and the circadian clock.

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

Genome information of humans showing abnormal sleep/wake pattern have identified mechanism of sleep and the circadian clock. A mutation in FAD binding domain of *hCRY2,* one of core clock genes, caused advanced sleep phase by altering binding of hCRY2 and FAD (Hirano et al., eLife, 2016). In this study, we found indicated FAD binding to CRY2 antagonizes FBXL3, which is E3 ubiquitin ligase promoting CRY2 degradation. The balance between FAD (stabilization) and FBXL3 (degradation) mediates proper CRY2 protein expression rhythms. As CRY2 acts as transcriptional repressor targeting many genes including metabolism-related genes, disfunction of CRY2 expression by inhibition of FAD synthesis caused abnormal glucose metabolism. Our study showed how metabolism is regulated by the circadian clock, which can be applicable for therapy of metabolic syndrome.

*13. Mieda M, Ono D, Hasegawa E, Okamoto H, Honma K, Honma S, Sakurai T (2015) Cellular clocks in AVP neurons of the SCN are critical for interneuronal coupling regulating circadian behavior rhythm. *Neuron.* **4;85**(5):1103-16.

Suprachiasmatic nucleus in the hypothalamus is center of the circadian clock and contributes to rhythmic sleep behavior in mammals. SCN consists of several kinds of neurons characterized by neuropeptides, while the function of each neuron has not been clearly understood. Here, we utilized Cre driver mouse lines combined with *Bmal1* (one of core clock genes) flox mice and analyzed the effect of clock disfunction in specific neurons in mouse behavioral rhythms. We demonstrated that knockout of *Bmal1* in AVP producing neurons caused lengthened circadian period and weakened cellular coupling among SCN neurons. This report is a pioneer study to determine the function of specific neurons in the SCN in sleep regulation and advanced understanding of the heterogeneity of the clock center, SCN.

14. Lee IT, Chang AS, Manandhar M, Shan Y, Fan J, Izumo M, Ikeda Y, Motoike T, Dixon S, Seinfeld JE, Takahashi JS, Yanagisawa M (2015) Neuromedin S-Producing Neurons Act as Essential Pacemakers in the Suprachiasmatic Nucleus to Couple Clock Neurons and Dictate Circadian Rhythms. *Neuron.* **85**(5):1086-102 doi:10.1016/j.neuron.2015.02.006

SCN acts as a pacemaker of the circadian clock. Although SCN is heterogenous neuronal populations, which neurons are important to generate circadian rhythms has been unknown. In this study, we identified *Neuromadin S* (*Nms*)-producing cells in SCN are essential for rhythmic sleep/wake behavior. We used *Nms-Cre* driver mice and precisely analyzed the effect of clock disfunction and inhibition of synaptic transmission in *Nms* neurons on the circadian rhythms. We demonstrated that synaptic transmission in Nms neurons has an important role for synchrony of the circadian phase among SCN neurons, contributing to normal

sleep/wake pattern.

*[7] **Applying the functional connections between sleep and memory for future therapy**

15. Takeuchi T, Duszkiewicz AJ, Sonneborn A, Spooner PA, Yamasaki M, Watanabe M, Smith CC, Fernández G, Deisseroth K, Greene RW, Morris RG (2016) Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature.* **537**(7620):357-362.

Exposure to a novel context can enhance the retention of everyday memories. The dopaminergic neurons mediating this phenomenon were believed to originate from the tyrosine-hydroxylase-expressing (TH+) neurons in the ventral tegmental area. In contrast to this idea, Takeuchi et al. show compelling evidence that this TH+ neurons in the locus coeruleus (LC), a region typically defined by noradrenergic signaling to the hippocampus, is responsible for the dopamine-dependent novelty effect. This finding changes the conventional idea of both the mechanisms of the novelty effect and the function of LC.

*16. Purple R, Sakurai T, Sakaguchi M (2017) Auditory conditioned stimulus presentation during NREM sleep impairs fear memory in mice. *Sci Rep.* **7**:46247.

Our memory is largely affected by sleep. However, the mechanisms linking both are still poorly understood. One reason for this is because many experimental approaches to disturb sleep also greatly stress subjects, which can, in turn, affect learning. Purple et al. approached sleep and memory interaction without changing the normal sleep architecture. They demonstrate that presting memory related sound during slow-wave sleep can modulate the fear memory. Animals exposed to the sound during non-REM sleep show a weaker association of the fearful experience with the sound in contrast to an animal that did not. These results provide solid evidence that memory can be manipulated during sleep and have potential applications in the treatment of PTSD.

*17. Soya S, Takahashi TM, McHugh TJ, Maejima T, Herlitze S, Abe M, Sakimura K, Sakurai T (2017) Orexin modulates behavioral fear expression through the locus coeruleus. *Nat Commun.* **8**(1):1606.

Orexin neurons in the lateral hypothalamus constitute a central feedback mechanism for feeding, and also are essential for vigilance. By integrating connectome and optogenetic analysis, Soya et al. provide compelling evidence that orexin neurons control fear memory expression through the noradrenergic neurons in the locus coeruleus, which in turn project to the lateral amygdala, the key center for emotional memory. Stimulation of this pathway induced memory generalization, which is a signature of PTSD symptoms. Interestingly, the authors showed that fasting, a manipulation to enhance orexinergic tones, potentiated the memory expression through this pathway, which may provide an essential mechanism for survival by remembering nourishing related information in starving environments.

*[8] **Orexin to locus coeruleus pathway gates fear-related behavior.**

*18. Soya S, Takahashi TM, McHugh TJ, Maejima T, Herlitze S, Abe M, Sakimura K, Sakurai T (2017) Orexin modulates behavioral fear expression through the locus coeruleus. *Nat Commun.* **8**(1): 1606.

Noradrenergic neurons in the locus coeruleus (NA^{LC}neurons) projecting to the lateral amygdala (LA) receive synaptic input from orexin neurons. Pharmacogenetic/optogenetic silencing of this circuit as well as acute blockade of the orexin receptor-1 (OX1R) decreases conditioned fear responses. In contrast, optogenetic stimulation of this circuit potentiates freezing behavior against a similar but distinct context or cue. Increase of orexinergic tone by fasting also potentiates freezing behavior and LA activity. These findings demonstrate the c orexin $\rightarrow$ NA^{LC} $\rightarrow$ LA pathway mediates fear-related behavior and suggests inappropriate excitation of this pathway may cause fear generalization sometimes seen in psychiatric disorders, such as PTSD.

*[9] **A forward genetics screen to uncover the molecular basis of innate fear in mice**

*19. Wang YB, Cao LQ, Lee CY, Matsuo T, Wu KJ, Asher G, Tang LJ, Saitoh T, Russell J, Klewe-Nebenius D, Wang L, Soya S, Hasegawa E, Cherasse Y, Zhou JM, Li YWB, Wang T, Zhan XW, Miyoshi C, Irukayama Y, Cao J, Meeks JP, Gautron L, Wang ZQ, Sakurai K, Funato H, Sakurai T, Yanagisawa M, Nagase H, Kobayakawa R, Kobayakawa K, Beutler B, Liu QH (2018) Large-scale forward genetics screening identifies Trpa1 as a chemosensor for predator odor-evoked innate fear behaviors. *Nat Commun.* **9**:2041.

Innate behaviors are genetically encoded, but the molecular bases of innate behaviors remain largely unknown. Predator odor 2,4,5-trimethyl-3-thiazoline (TMT) and its potent analog 2-methyl-2-thiazoline (2MT) elicit innate fear/defensive behaviors in naïve mice. Here, we conduct a large-scale forward genetics screen of ethylnitrosourea (ENU)-mutagenized mice. We find that loss of Trpa1, a pungency/irritancy receptor, diminishes TMT/2MT and snake skin-evoked innate fear/defensive responses. Moreover, Trpa1 acts as a chemosensor for 2MT/TMT and Trpa1-expressing trigeminal ganglion neurons contribute critically to 2MT-evoked freezing. The work establishes the first forward genetics screen to uncover the molecular basis of innate fear, a basic emotion and conserved survival mechanism.

*[10] **Adenosine A_1 and A_{2A} receptors have essential yet different roles in sleep gating and function**

*20. Korkutata M, Saitoh T, Cherasse Y, Ioka S, Duo F, Qin R, Murakoshi N, Fujii S, Zhou X, Sugiyama F, Chen JF, Kumagai H, Nagase H, Lazarus M (2018) Enhancing endogenous adenosine A2A receptor signaling induces slow-wave sleep without affecting body temperature and cardiovascular function. *Neuropharmacology.* **44**:122-132

Insomnia is one of the major sleep problems with an estimated prevalence of 10% to 15% in the general population and 30% to 60% in the older population. The Lazarus/Oishi lab succeeded in identifying a positive allosteric modulator for $A_{2A}R$ and demonstrated that enhancing $A_{2A}R$ signaling induces sleep that is indistinguishable from the major component of natural sleep, known as slow-wave sleep, as it is characterized by slow and high-voltage brain waves. In contrast to the $A_{2A}R$ agonists, the $A_{2A}R$ positive allosteric modulator does not affect blood pressure, heart rate or body temperature. 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. Allosteric modulators of $A_{2A}R$ may help people with sleep problems to fall asleep.

21. Bjorness TE, Dale N, Mettlach G, Sonneborn A, Sahin B, Fienberg AA, Yanagisawa M, Bibb JA, Greene RW (2016) An Adenosine-Mediated Glial-Neuronal Circuit for Homeostatic Sleep. *J Neurosci.* **36**(13):3709-21.

In this paper, Greene and colleagues provides evidence for adenosine-mediated regulation of the homeostatic sleep need via activation of neuronal A1R controlled by glial adenosine kinase (AdK), an enzyme that effectively controls the intracellular adenosine concentration. Mice deficient in neuronal A1R's do not have a homeostatic sleep response to sleep loss. Mice deficient in glial AdK exhibit increased homeostatic sleep response to sleep loss. Thus glial metabolism of adenosine controls adenosine-mediated activation of neuronal A1R's.

[11] **Clarification of a mystery to scratch skin on feeling itch: Role of spinal dynorphin**

22. Kardon AP, Polgár E, Hachisuka J, Snyder LM, Cameron D, Savage S, Cai X, Karnup S, Fan CR, Hemenway GM, Bernard CS, Schwartz ES, Nagase H, Schwarzer C, Watanabe M, Furuta T, Kaneko T, Koerber HR, Todd AJ, Ross SE (2015) Dynorphin acts as a neuromodulator to inhibit itch in the dorsal horn of the spinal cord.

Neuron. **82**(3):573-86

Bhlhb5, a transcription factor, is expressed in a specific population of interneuron (B5-I neuron) in superficial dorsal horn of the spinal cord. Mice lacking *Bhlhb5* display the lack of B5-I neurons in the spinal cord and develop pathological itching. This paper neurochemically characterizes that majority of B5-I neurons expresses dynorphin, an endogenous kappa opioid peptide, from early developmental stage in mice and deletion of *Bhlhb5* almost completely lacks dynorphin of B5-I neurons in the adult spinal cord. Furthermore, basic antipruritics, such as menthol and capsaisin, inhibit neural pathway of itch and its related behaviors through electrophysiologically activated B5-I neurons in the spinal cord. However, *Bhlhb5*$^{-/-}$ mice show no significant inhibition of itch by menthol. In contrast, kappa opioid agonist nalfurafine significantly inhibits itch in response to variety of pruritogens, and also inhibits *Bhlhb5*$^{-/-}$-induced itch sensation.

*[12] **Detailed description of energy metabolism during human sleep**

*23. Kayaba M, Park I, Iwayama K, Seya Y, Ogata H, Yajima K, Satoh M, Tokuyama K (2017) Energy metabolism differs between sleep stages and begins to increase prior to awakening. *Metab Clin Exp.* **69**:14-23.

Human sleep is generally 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, the present study revealed dynamic characteristics of sleeping energy metabolism. Key findings addressing the interactions between sleep and metabolism in normal subjects warrant further studies in pathological conditions such as patients with obstructive sleep apnea, sleep under the effect of hypnotic agents, etc.

*[13] **The mechanistic therapy of narcolepsy: proof-of-concept**

*24. Nagahara T, Saitoh T, Kutsumura N, Irukayama-Tomobe Y, Ogawa Y, Kuroda D, Gouda H, Kumagai H, Fujii H, Yanagisawa M, Nagase H (2015) Design and Synthesis of Non-Peptide, Selective Orexin Receptor 2 Agonists. *J Med Chem.* **58**:7931–7937.

Since the discovery that the sleep disorder narcolepsy is caused by loss of orexin back in early 2000's, intensive efforts had been made to design non-peptide orexin receptor agonists. However, this turned out to be extremely challenging. This paper describes the discovery of the world's first small-molecule orexin receptor agonist. This is an orthosteric full agonist with nanomolar affinities for OX2R, and a 70-fold selectivity for OX2R over OX1R; OX2R is the main orexin receptor involved in sleep/wake regulation. This paper demonstrated for the first time that such agonists can indeed be designed, providing a basis for orexin replacement therapy.

*25. Irukayama-Tomobe Y, Ogawa Y, Tominaga H, Ishikawa Y, Hosokawa N, Ambai S, Kawabe Y, Uchida S, Nakajima R, Saitoh T, Kanda T, Vogt K, Sakurai T, Nagase H, Yanagisawa M (2017) Nonpeptide orexin type-2 receptor agonist ameliorates narcolepsy-cataplexy symptoms in mouse models. *Proc Natl Acad Sci USA.* **114**(22): 5731-5736.

This paper reports the detailed pharmacology of one of the compounds described in the previous paper, YNT-185, showing that it is a highly potent OX2R-selective agonist. Importantly, YNT-185 potently inhibits sleep-onset REM periods (a marker for cataplectic attacks) in orexin-null mice and induces wakefulness in wildtype mice. These pharmacological effects were abolished in orexin receptor-deficient mice, showing the specificity. Moreover, the orexin receptor agonist did not show tachyphylaxis upon repeated administrations over 7 nights. The paper provides a solid proof-of-concept for the mechanistic therapy of orexin-deficient narcolepsy using orexin receptor agonists.

*26. Kaushik MK, Aritak, K, Imanishi A, Kanbayashi T, Ichikawa T, Shimizu T, Urade Y, Yanagisawa M (2018) Continuous intrathecal orexin delivery inhibits cataplexy in a murine model of narcolepsy. *Proc Natl Acad Sci USA.* **115**(23): 6046-6051.

Our previous studies had shown that central bolus administration of orexin peptide can ameliorate narcolepsy symptoms in orexin-null mice. However, intracerebroventricular administration would be highly difficult in clinical settings. In contrast, chronic intrathecal drug infusion through an implantable pump is a clinically available strategy to treat a number of neurological diseases. In this paper, we show that the narcoleptic symptoms of orexin-null mice can be ameliorated by continuous intrathecal orexin delivery at the lumbar level. This report provides a proof-of-concept for a strategy for mechanistic therapy of narcolepsy through intrathecal orexin delivery by implantable minipump.

*[14] **The neuropeptide orexin as a potential anti-inflammatory therapeutic for septic shock**

*27. Ogawa Y, Irukayama-Tomobe Y, Murakoshi N, Kiyama M, Ishikawa Y, Hosokawa N, Tominaga H, Uchida S, Kimura S, Kanuka M, Morita M, Hamada M, Takahashi S, Hayashi Y, Yanagisawa M (2016) Peripherally administered orexin improves survival of mice with endotoxin shock. *eLife.* **5**: e21055.

Septic shock, a fulminant systemic immune response, is an intractable problem caused by infection often in gravely ill or elderly patients. This paper shows that peripheral injection of the neuropeptide orexin may constitute a novel therapeutic strategy for sepsis. Although peripherally administered orexin does not normally permeate the blood-brain barrier, under the systemic inflammatory condition it goes into the brain and exert multi-pronged anti-inflammatory actions by acting in the CNS. This study demonstrates an unexpected potential utility of the orexin peptide as a therapeutic drug. It also highlights the powerful regulation of immune responses by the brain.

[15] **Experimental dissociation of sleep homeostasis and emotionally/motivationally induced wakefulness**

28. Suzuki A, Sinton CM, Greene RW, Yanagisawa M (2013) Behavioral and biochemical dissociation of arousal and homeostatic sleep need influenced by prior wakeful experience in mice. *Proc Natl Acad Sci USA.* **110**(25):10288-93

In this paper, in order to demonstrate dissociation of wakefulness induced by emotional/motivational stimuli and accumulation of homeostatic sleep need, mice are subjected to two different kinds of sleep deprivation: i) by traditional gentle handling, in which the mice are “passively” awake; and ii) by continually exposing the mice to novel environment by cage change, in which the mice are “spontaneously” awake because they are motivationally stimulated. Indeed, whereas the non-REM EEG delta power, the most reliable index of homeostatic sleep need, was similarly elevated after either scheme i) or ii), the sleep latency upon release from sleep deprivation was very short in scheme i) but long and similar to non-sleep-deprived mice in scheme ii). This behavioral dissociation of arousal from sleep homeostasis was also backed by biochemical dissociation in terms of a set of phosphoprotein markers. The finding formed a fundamental basis for later studies at IIIS.

Appendix1-2 List of Papers of Representative of Interdisciplinary Research Activities

* List **up to 10 papers** underscoring each interdisciplinary research activity and give brief accounts (within 10 lines).
* For each, write the author name(s); year of publication; journal name, volume, page(s), and article title. Any listing order may be used as long as format is the same. If a paper has many authors, underline those affiliated with the Center.
* If a paper has many authors (say, more than 10), all of their names do not need to be listed.

1. Korkutata M, Saitoh T, Cherasse Y, Ioka S, Duo F, Qin R, Murakoshi N, Fujii S, Zhou X, Sugiyama F, Chen JF, Kumagai H, Nagase H, Lazarus M et al. (2018) Enhancing endogenous adenosine A_2A receptor signaling induces slow-wave sleep without affecting body temperature and cardiovascular function. *Neuropharmacology.* **44**:122-132

   Insomnia is one of the major sleep problems with an estimated prevalence of 10% to 15% in the general population. Moreover, insomnia frequently co-occurs with a wide range of psychiatric disorders, including depression and anorexia. The most widely prescribed agents for the treatment of insomnia are benzodiazepines and non-benzodiazepines, which are plagued by a wide range of adverse effects. In recent years, remarkable progress has been made in the discovery of ligands that act at allosteric sites to regulate receptor function with more selectivity. On the basis of close collaboration, the Lazarus/Oishi lab (Neuropharmacology) and Nagase lab (Medicinal Chemistry) succeeded in identifying the first positive allosteric modulator for adenosine A_2A receptors (A_2AR) that induces natural sleep. Allosterically enhancing A_2AR signaling may provide a new therapeutic avenue for treating insomnia.

2. Wang ZQ, Ma J, Miyoshi C, Lie YX, Sato M, Ogawa Y, Lou TT, Ma CY, Gao X, Lee C, Fujiyama T, Yang XJ, Zhou S, Hotta-Hirashima N, Klewe-Nebenius D, Ikkyu A, Kakizaki M, Kanno S, Cao LQ, Takahashi S, Peng JM, Yu YH, Funato H, Yanagisawa M, Liu QH (2018) Quantitative phosphoproteomic analysis of the molecular substrates of sleep need. *Nature.* **558**(7710):435-439.

   We performed quantitative proteomic and phosphoproteomic analysis of whole mouse brain from two opposite models of increased sleep need. Sleep deprivation induces cumulative phosphorylation of brain proteome, which dissipates during recovery sleep. Strikingly, *Sleepy* (*Sik3*$^{Slp/+}$) mutant brains exhibit a hyper-phosphoproteome mimicking sleep-deprived brains, owing to a gain-of-function mutation of protein kinase SIK3^{14}. Cross-comparison of two models identified 80 mostly synaptic Sleep-Need-Index-PhosphoProteins (SNIPPs), whose phosphorylation states closely parallel changes of sleep need. Mutant SLEEPY/SIK3 kinase preferentially associated with and phosphorylated SNIPPs. Our studies suggest that the phosphorylation/dephosphorylation cycle of SNIPPs may represent a major regulatory mechanism that underlies both synaptic homeostasis and sleep homeostasis.

3. Wang YB, Cao LQ, Lee CY, Matsuo T, Wu KJ, Asher G, Tang LJ, Saitoh T, Russell J, Klewe-Nebenius D, Wang L, Soya S, Hasegawa E, Cherasse Y, Zhou JM, Li YWB, Wang T, Zhan XW, Miyoshi C, Irukayama Y, Cao J, Meeks JP, Gautron L, Wang ZQ, Sakurai K, Funato H, Sakurai T, Yanagisawa M, Nagase H, Kobayakawa R, Kobayakawa K, Beutler B, Liu QH (2018) Large-scale forward genetics screening identifies Trpa1 as a chemosensor for predator odor-evoked innate fear behaviors. *Nat Commun.* **9**:2041

   Innate behaviors are genetically encoded, but the molecular bases of innate behaviors remain largely unknown. Predator odor 2,4,5-trimethyl-3-thiazoline (TMT) and its potent analog 2-methyl-2-thiazoline (2MT) elicit innate fear/defensive behaviors in naïve mice. Here, we conduct a large-scale forward genetics screen of ethylnitrosourea (ENU)-mutagenized mice. We find that loss of Trpa1, a pungency/irritancy receptor, diminishes TMT/2MT and snake skin-evoked innate fear/defensive responses. Moreover, Trpa1 acts as a chemosensor for 2MT/TMT and Trpa1-expressing trigeminal ganglion neurons contribute critically to 2MT-evoked freezing. The work establishes the first forward genetics screen to uncover the molecular basis of innate fear, a basic emotion and conserved survival mechanism.

4. Toyama S, Shimoyama N, Tagaito Y Nagase H, Saitoh T, Yanagisawa M, Shimoyama M. (2018) Nonpeptide Orexin-2 Receptor Agonist Attenuates Morphine-induced Sedative Effects in Rats. *Anesthesiology.* **128**(5):992-1003.

   Sleepiness and decrease in attention are dose-limiting side effects of opioids. The orexin system plays an important role in maintaining wakefulness. This study aimed to explore the potential of orexin receptor agonists to alleviate morphine-induced sedative effects. Morphine sedative effects were evaluated as changes in EEG, locomotor activity, and acoustic startle response in rats. Orexin A and the non–peptide selective OX_2R agonist, YNT-185, attenuated morphine-induced EEG changes in rats and behavioral manifestation of morphine sedative effects. However, orexin receptor agonists did not affect the analgesic effect of morphine. These results suggest that the activation of OX_2R alleviates morphine-induced sedative effects. The non–peptide selective OX_2R agonists may be a promising candidate to treat the undesirable side effects of opioids.

5. Saitoh A, Tominaga H, Ogawa Y, Irukayama-Tomobe Y, Yamada M, Yanagisawa M, Nagase H (2018) Effects of the delta opioid receptor agonist KNT-127 on electroencephalographic activity in mice. *Pharmacol Rep.* **70**(2):350-354.

   Several lines of evidence indicate that delta opioid receptor (DOR) agonists induce convulsive behaviors and catalepsy-like behaviors in rodents and monkeys in vivo study. This paper presents that the our novel selective DOR agonist KNT-127 did not induce convulsion-like behaviors and convulsion-like electroencephalographic (EEG) disturbance in mice, while prototypic DOR agonist SNC-80 induces convulsion-like behaviors with catalepsy and EEG disturbance in mice. Thus, this paper clearly demonstrates that our novel compound KNT-127 should be a candidate compound for the development of improved DOR-based psychotropic drug without convulsive properties.

6. Orui S, Yamamoto N, Saitoh T, Kutsumura N, Nagumo Y, Irukayama-Tomobe Y, Ogawa Y, Ishikawa Y, Watanabe Y, Hayakawa D, Gouda H, Yanagisawa M, Nagase H (2018) Essential structure of orexin 1 receptor antagonist YNT-707, Part II:Drastic effect of the 14-hydroxy group on the orexin 1 receptor antagonistic activity. *Bioorg Med Chem Lett.* **28**(4):774-777.

   The 14-dehydrated and 14-H derivatives of the orexin 1 receptor (OX_1R) antagonist YNT-707 with a 6β-amide side chain showed stronger activities for OX_1R than the corresponding 14-hydroxy derivatives. The conformational analyses suggested that the 17-benzenesulfonyl groups in the 14-dehydrated and 14-H derivatives tended to be located toward the upper side of the D-ring compared with that in the 14-hydroxy derivatives. The 14-dehydrated derivative with the 6α-amide side chain showed more potent antagonistic activity for OX_1R than the corresponding 14-hydroxy derivative, while the corresponding 14-H derivative was only slightly stronger. Thus, we clarified that the 14-hydroxy group in the 4,5-epoxymorphinans decreased the antagonistic activity for OX_1R.

7. Yamamoto N, Orui S, Okada T, Yata M, Saitoh T, Kutsumura N, Nagumo Y, Irukayama-Tomobe Y, Ogawa Y, Ishikawa Y, Watanabe Y, Hayakawa D, Gouda H, Yanagisawa M, Nagase H (2017) Essential structure of orexin 1 receptor antagonist YNT-707, Part I: Role of the 4,5-epoxy ring for binding with orexin 1 receptor. *Bioorg Med Chem Lett.* **27**(17): 4176-4179.

   We focused on the selective orexin 1 receptor (OX_1R) antagonist YNT-707 with a 4,5-epoxymorphinan skeleton. The roles of both the 3-methoxy group and the 4,5-epoxy ring and the orientation of the 6-amide side chain in YNT-707 were investigated. The 3-methoxy group was essential for the OX_1R antagonistic activity, while the 4,5-epoxy ring was not. However, the 4,5-epoxy ring would play an important role for the orientation of the 6-amide side chain which was located to the down side of the C-ring. We proposed that the active conformation of YNT-707 and its derivatives for OX_1R would be deeply related to the orientation of the 6-amide side chain in the 4,5-epoxymorphinan skeletons.

8. Irukayama-Tomobe Y, Ogawa Y, Tominaga H, Ishikawa Y, Hosokawa N, Ambai S, Kawabe Y, Uchida S, Nakajima R, Saitoh T, Kanda T, Vogt K, Sakurai T, Nagase H, Yanagisawa M (2017)

Nonpeptide orexin type-2 receptor agonist ameliorates narcolepsy-cataplexy symptoms in mouse models. *Proc Natl Acad Sci USA.* **114**(22): 5731-5736.

Although “academic” collaborations between biology and chemistry labs are commonplace today, WPI-IIIS is unique in that it embraces true medicinal chemistry efforts (those aiming at serious development of potential pre-clinical leads) in the academia, by fusing the chemistry efforts of designing and synthesizing drug-like compounds with the pharmacological verification of compounds' in vitro and in vivo efficacies. This paper eloquently represents a fruit of such fusion efforts. Ever since the discovery in late 1990's to early 2000's that narcolepsy is an orexin-deficiency syndrome, a huge amount of efforts had been made, especially in the industry, to develop small-molecule orexin receptor agonists. This turned out to be extremely challenging, and most parties dropped out of these efforts. At WPI-IIIS, we endured by fusing the cutting-edge drug design expertise of Nagase (who previously discovered two marketed, first-in-class medicines) with pharmacological expertise of Yanagisawa (who discovered orexin and then found narcolepsy in orexin-null mice).

9. Nagase H, Yamamoto N, Yata M, Orui S, Okada T, Saitoh T, Kutsumura N, Nagumo Y, Irukayama-Tomobe Y, Ishikawa Y, Ogawa Y, Hirayama S, Kuroda D, Watanabe, Gouda H, Yanagisawa M (2017) Design and Synthesis of Potent and Highly Selective Orexin 1 Receptor Antagonists with a Morphinan Skeleton and Their Pharmacologies. *J Med Chem.* **60**(3): 1018-1040.

A κ opioid receptor agonist nalfurafine was found to be an antagonist activity toward the orexin 1 receptor (OX_1R) (K_i = 250 nM). Methylation of the phenolic 3-hydroxy group and conversion of the 17-cyclopropylmethyl group to an aryl sulfonyl group in the 4,5-epoxymorphinan skeleton enhanced antagonistic activity for OX_1R. Moreover, modification of the furan ring to the pyridine ring (2-pyridyl group) in the 6-side chain afforded compound 71 (YNT-1310; OX_1R: K_i = 1.36 nM, OX_2R: not active), and its dihydrosulfate was highly water-soluble. The compound 71·2H2SO4 showed almost no affinity for opioid receptors and attenuated the physical dependence of morphine. These results suggest that nalfurafine derivatives could be a useful lead compounds to develop highly selective OX_1R antagonists and clarify the relationship between KOR and OX_1R.

10. Nagahara T, Saitoh T, Kutsumura N, Irukayama-Tomobe Y, Ogawa Y, Kuroda D, Gouda H, Kumagai H, Fujii H, Yanagisawa M, Nagase H (2015) Design and Synthesis of Non-Peptide, Selective Orexin Receptor 2 Agonists. *J Med Chem.* **58**: 7931-7937.

Orexins are a family of neuropeptides that regulate sleep/wakefulness, acting on two G-protein-coupled receptors, orexin receptors 1 (OX_1R) and 2 (OX_2R). Genetic and pharmacologic evidence suggests that orexin receptor agonists, especially OX_2R agonist, are useful for mechanistic therapy of the sleep disorder narcolepsy/cataplexy (narcolepsy type I). A high throughput screening identified some hit compounds that possess aryl sulfonamide structure. Based on these structures, Hit to Lead study was conducted and discovered a potent and OX_2R-selective agonist (EC50 on OX2R is 23 nM, OX_1R/OX_2R EC50 ratio is 70). The intracerebroventricular administration of the agonist increased wake time in wild-type mice but not in receptor knockout mice. This discovery opens up new avenues for therapies related to the activation of the orexin system, especially with respect to the treatment of sleep disorders such as narcolepsy.

Appendix 1-3
Major Awards, Invited Lectures, Plenary Addresses (etc.) (within 2 pages)

*Prepare the information below during the period from the start of the center through March 2019.

1. Major Awards

*List main internationally-acclaimed awards received/unofficially announced in order from the most recent.
*For each, write the recipient's name, the name of award, and the date issued.
In case of multiple recipients, underline those affiliated with the center.

Date	Recipient's name	Name of award
Sep 13, 2018	Masashi Yanagisawa	The Keio Medical Science Prize (Keio University Medical Science Fund)
May 30, 2018	Yo Oishi	The Encouraging Prize (Japanese Society of Sleep Research)
Jan 4, 2018	Masashi Yanagisawa	The Asahi Prize (The Asahi Shimbun Company)
Nov 30,2017	Masashi Yanagisawa, Hiromasa Funato	Erwin von Bälz Preis (Boehringer Ingelheim Japan, Inc.)
Jul 10, 2017	Takeshi Sakurai	The Shiono Prize (The Cell Science Research Foundation)
Apr 11, 2017	Yu Hayashi	The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology The Young Scientists' Prize (Ministry of Education, Culture, Sports, Science and Technology)
Nov 22, 2016	Yu Hayashi	The Tsukuba Encouragement Prize (The Science and Technology Promotion Foundation of Ibaraki)
Oct 25, 2016	Joseph Takahashi	Peter C. Farrell Prize in Sleep Medicine (Harvard Medical School Division of Sleep Medicine)
May 13, 2016	Yu Hayashi	The Encouraging Prize (Japanese Society of Sleep Research)
Apr 28, 2016	Masashi Yanagisawa	Medal with Purple Ribbon (Cabinet Office, Government of Japan)
Oct 6, 2015	Akiyoshi Fukamizu	Jokichi Takamine Memorial Award (The Society of Cardiovascular Endocrinology and Metabolism)
Mar 28, 2015	Masashi Yanagisawa	The Walter B. Cannon Memorial Award (American Physiological Society)
Sep 24, 2014	Hiroshi Nagase	Yamazaki Teiichi Prize (Foundation for Promotion of Material Science and Technology of Japan)
Nov 26, 2013	Junichi Hayashi	Tsukuba Award (The Science and Technology Promotion Foundation of Ibaraki)
Nov 22, 2013	Masashi Yanagisawa	Jokichi Takamine Memorial Award (The Society of Cardiovascular Endocrinology and Metabolism)
Jun 18, 2013	Hiroshi Nagase	National Commendation for Invention –the Invention Prize (Japan Institute of Invention and Innovation)
Mar 22, 2013	Hiroshi Nagase	Okochi Memorial Technology Prize (Okochi Memorial Foundation)
Apr 1, 2013	Takeshi Sakurai	The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology (Ministry of Education, Culture, Sports, Science and Technology)

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

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

Date(s)	Lecturer/Presenter's name	Presentation title	Conference name
Nov 10, 2018	Masashi Yanagisawa	Keynote Lecture: "Toward the Mysteries of Sleep/ What makes you sleepy? Elusive molecular substrates for homeostatic sleep need"	The 3rd Japan-US Science Forum in Boston 2018/Sleep Grand Rounds (Cambridge, USA)
Sep 28, 2018	Qinghua Liu	"Quantitative phosphoproteomic analysis of the molecular substrates of sleep need"	The 24th Congress of the European Sleep Research Society (Basel, Switzerland)
Sep 11, 2018	Masashi Yanagisawa	Keynote Lecture: "Orexin agonism as a potential mechanistic therapy for narcolepsy/ cataplexy"	7th International Narcolepsy Symposium (Beverly, USA)
Jul 7-11, 2018	Michael Lazarus	"The link between REM sleep loss and the desire for junk food"	11th FENS Forum of Neuroscience (Berlin, Germany)
Jul 7-11, 2018	Yu Hayashi	"The mystery of rapid eye movement sleep: New circuits and insights"	11th FENS Forum of Neuroscience (Berlin, Germany)
Mar 18-23, 2018	Qinghua Liu	Plenary Lecture: "Cumulative Phosphorylation of SNIPPs as a Function of Sleep Need"	Gordon Research Conference on Sleep Regulation and Function (Galveston, USA)
Oct 4-7, 2017	Masashi Yanagisawa	Special Lecture: "Highlights of ET-15"	15th International Conference on Endothelin (Prague, Czech)
May 19-21, 2017	Takeshi Sakurai	Plenary Speaker: "The Mechanism of Narcolepsy: what it tells on clinical perspectives?"	The 2nd International Taiwanese Congress of Neurology (Taipei, Taiwan)
Aug 30, 2016	Hiroshi Nagase	"The science and the development of non-addictive opioid receptor agonists"	76th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2016 (Buenos Aires, Argentina)
Jun 8, 2015	Masashi Yanagisawa	Plenary Session: "Toward solving the mystery of sleep: From reverse genetics to forward genetics in mice"	Sleep2015 (Seattle, USA)

Appendix 1-4 2018 List of Center's Research Results

Refereed Papers

- List only the Center's papers published in 2018. (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. As some WPI-affiliated authors of papers published up to 2011 may not be aware of this requirement, their papers are treated as "WPI-related papers." From 2012, 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 20), 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) 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.

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

A. WPI papers

1. Original Articles

1) Nakamura Y, Matsuzaka, T, Tahara-Hanaoka S, Shibuya K, Shimano H, Nakahashi-Oda C, Shibuya A (2018) Elovl6 regulates mechanical damage-induced keratinocyte death and skin inflammation. Cell Death & Disease 9:1181. doi:10.1038/s41419-018-1226-1

2) Bjorness TE, Greene RW (2018) Sleep deprivation alters the time course but not magnitude of locomotor sensitization to cocaine. *Sci Rep.* **8**:17672. doi:10.1038/s41598-018-36002-1

3) Miyagawa T, Khor SS, Toyoda H, Kanbayashi T, Mishima K, Honda M, Tokunaga K et al. (2018) A variant at 9q34.11 is associated with HLA-DQB1*06:02 negative essential hypersomnia. *J. Hum. Genet.* **63**(12):1259-1267 doi:10.1038/s10038-018-0518-8

4) Saito YC, Tsujino N, Abe M, Yamazaki M, Sakimura K, Sakurai T (2018) Serotonergic Input to Orexin Neurons Plays a Role in Maintaining Wakefulness and REM Sleep Architecture. *Front Neurosci.* **12**:892 doi:10.3389/fnins.2018.00892

5) Takata Y, Oishi Y, Zhou XZ, Hasegawa E, Takahashi K, Cherasse Y, Sakurai T, Lazarus M (2018) Sleep and Wakefulness Are Controlled by Ventral Medial Midbrain/Pons GABAergic Neurons in Mice. *J Neurosci.* **38**(47):10080-10092. doi:10.1523/JNEUROSCI.0598-18.2018

6) Azami T, Matsumoto K, Jeon H, Waku T, Muratani M, Niwa H, Takahashi S, Ema M (2018) Klf5 suppresses ERK signaling in mouse pluripotent stem cells. *PLoS One* **13**(11):e0207321 doi:10.1371/journal.pone.0207321

7) Saitoh A, Soda A, Kayashima S, Yoshizawa K, Oka JI, Nagase H, Yamada M (2018) A delta opioid receptor agonist, KNT-127, in the prelimbic medial prefrontal cortex attenuates glial glutamate transporter blocker-induced anxiety-like behavior in mice. *J Pharmacol Sci.* **138**(3):176-183. doi:10.1016/j.jphs.2018.09.009

8) Kaushik MK, AritakeK, Cherasse Y, Sharma R, Urade Y (2018) A gain-of-function study of amelioration of pentylenetetrazole-induced seizures by endogenous prostaglandin D-2 *Neurosci Lett.* **686**:140-144. doi:10.1016/j.neulet.2018.09.011

9) Kutsumura N, Nagase H (2018) Unique Reactions of Morphinan Skeletons and Conversions of the Skeletons to Active Alkaloids. *J Syn Org Chem Jpn.* [Japanese: 有機合成化学協会誌] **76**(9):914-921. doi:10.5059/yukigoseikyokaishi.76.914

10) Kutsumura N, Okada T, Imaide S, Fujii H, Nagase H (2018) Acetic Anhydride Mediated Retro-Ene Reaction via a [4.4.3]Propellane Skeleton Intermediate Containing a Quaternary Ammonium Linkage. *Synthesis-Stuttgart* **50**(21):4263-4269. 10.1055/s-0036-1589138

11) Zhang Y, Sugai T, Yamamoto T, Yamamoto, N, Kutsumura N, Nishiyama S, Einaga Y, Saitoh, T, Nagase H (2018) Oxidative Cleavage of the Acyl-Carbon Bond in Phenylacetone with Electrogenerated Superoxide Anions. *ChemElectroChem.* **5**. 10.1002/celc.201801308.

12) Kuwano N, Kato, TA, Mitsuhashi M, Sato-Kasai M, Shimokawa N, Hayakawa K, Ohgidani M, Sagata N, Kubo H, Sakurai T, Kanba S (2018) Neuron-related blood inflammatory markers as an objective evaluation tool for major depressive disorder: An exploratory pilot case-control study. *J Affect Disorders.* **240**:88-98. doi:10.1016/j.jad.2018.07.040

13) Murata K, Lu WZ, Hashimoto M, Ono N, Muratani M, Nishikata K, Kim JD, Ebihara S, Ishida J, Fukamizu A (2018) PRMT1 Deficiency in Mouse Juvenile Heart Induces Dilated Cardiomyopathy and Reveals Cryptic Alternative Splicing Products. *iScience.* **8**:200-+. doi:10.1016/j.isci.2018.09.023

14) Sakikubo M, Furuyama K, Horiguchi M, Hosokawa S, Aoyama Y, Tsuboi K, Goto T, Hirata K, Masui T, Dor Y, Fujiyama T, Hoshino M, Uemoto S, Kawaguchi Y (2018) Ptf1a inactivation in adult pancreatic acinar cells causes apoptosis through activation of the endoplasmic reticulum stress pathway. *Sci Rep.* **8**:15812. doi:10.1038/s41598-018-34093-4

15) Cherasse Y, Aritake K, Oishi Y, Kaushik MK, Korkutata M, Urade Y (2018) The Leptomeninges Produce Prostaglandin D-2 Involved in Sleep Regulation in Mice. *Front Cell Neurosci.* **12**:357. doi:10.3389/fncel.2018.00357

16) Honda T, Fujiyama T, Miyoshi C, Ikkyu A, Hotta-Hirashima N, Kanno S, Mizuno S, Sugiyama F, Takahashi S, Funato H, Yanagisawa M (2018) A single phosphorylation site of SIK3 regulates daily sleep amounts and sleep need in mice *Proc Natl Acad Sci USA.* **115**(41):10458-10463. doi:10.1073/pnas.1810823115

17) Sugiyama, A, Yamada M, Saitoh A, Nagase H, Oka JI, Yamada M (2018) Administration of a delta opioid receptor agonist KNT-127 to the basolateral amygdala has robust anxiolytic-like effects in rats. *Psychopharmacology.* **235**(10):2947-2955. doi:10.1007/s00213-018-4984-7

18) Kulathunga K, Hamada M, Hiraishi Y, Otake M, Tran MTN, Cheng O, Tanaka J, Sakasai T, Sakaguchi S, Sugiyama Y, Fleischmann BK, Takahashi S, Miwa Y (2018) A Novel iRFP-Incorporated in vivo Murine Atherosclerosis Imaging System. *Sci Rep.* **8**:14515. doi: 10.1038/s41598-018-32456-5

19) Kutsumura N, Kiriseko A, Niwa K, Saito T (2018) Total Syntheses of 3-epi-Litsenolide D-2 and Lincomolide A. *J Org Chem.* **83**(18):11450-11457. doi:10.1021/acs.joc.8b01825

20) Mochizuki A, Nakayama K, Nakamura S, Dantsuji M, Kamijo R, Shioda S, Sakurai T, Ozeki M, Inoue T (2018) Involvement of orexin in lipid accumulation in the liver. *J Oral Sci.* **60**(3):76-82. doi:10.1016/j.job.2018.07.001

21) Takaya D, Inaka K, Omura, A, Takenuki K, Kawanishi M, Yabuki Y, Nakagawa Y, Tsuganezawa K, Ogawa N, Watanabe C, Honma T, Aritake K, Urade Y, Shirouzu M, Tanaka A (2018) Characterization of crystal water molecules in a high-affinity inhibitor and hematopoietic prostaglandin D synthase complex by interaction energy studies. *Bioorgan Med Chem.* **26**(16):4726-4734. doi:10.1016/j.bmc.2018.08.014

22) Niwa Y, Kanda GN, Yamada RG, Shi S, Sunagawa GA, Ukai-Tadenuma M, Fujishima H, Matsumoto N, Masumoto K, Nagano M, Kasukawa T, Galloway J, Perrin D, Shigeyoshi Y, Ukai H, Kiyonari H, Sumiyama K, Ueda HR (2018) Muscarinic Acetylcholine Receptors Chrm1 and Chrm3 Are Essential for REM Sleep. *Cell Reports.* **24**(9):2231. doi:10.1016/j.celrep.2018.07.082

23) Iwasaki K, Komiya H, Kakizaki M, Miyoshi C, Abe M, Sakimura K, Funato H, Yanagisawa M (2018) Ablation of Central Serotonergic Neurons Decreased REM Sleep and Attenuated Arousal Response. *Front Neurosci.* **12**:535. doi:10.3389/fnins.2018.00535

24) Shinohara R, Taniguchi M, Ehrlich AT, Yokogawa K, Deguchi Y, Cherasse Y, Lazarus M, Urade Y, Ogawa A, Kitaoka S, Sawas A, Narumiya S, Furuyashiki T (2018) Dopamine D1 receptor subtype mediates acute stress-induced dendritic growth in excitatory neurons of the medial prefrontal cortex and contributes to suppression of stress susceptibility in mice. *Mol Psychiatry.* **23**(8):1717-1730. doi:10.1038/mp.2017.177

25) Sato Y, Tsukaguchi H, Takahashi S, Yoshimura A et al. (2018) A mutation in transcription factor MAFB causes Focal Segmental Glomerulosclerosis with Duane Retraction Syndrome. *Kidney Int.* **94**(2):396-407. doi:10.1016/j.kint.2018.02.025

26) Yoshida S, Ohnishi R, Tsuneoka Y, Yamamoto-Mimura Y, Muramatsu R, Kato T, Funato H, Kuroda KO (2018) Corticotropin-Releasing Factor Receptor 1 in the Anterior Cingulate Cortex Mediates Maternal Absence-Induced Attenuation of Transport Response in Mouse Pups. *Front Cell Neurosci.* **12**:204. doi:10.3389/fncel.2018.00204

27) Saito YC, Maejima T, Nishitani M, Hasegawa E, Yanagawa Y, Mieda M, Sakurai T (2018) Monoamines Inhibit GABAergic Neurons in Ventrolateral Preoptic Area That Make Direct Synaptic Connections to Hypothalamic Arousal Neurons. *J Neurosci.* **38**(28):6366-6378. doi:10.1523/JNEUROSCI.2835-17.2018

28) Fujiyama T, Miyashita S, Tsuneoka Y, Kanemaru K, Kakizaki M, Kanno S, Ishikawa Y, Yamashita M, Owa T, Nagaoka M, Kawaguchi Y, Yanagawa Y, Magnuson MA, Muratani M, Shibuya A, Nabeshima Y, Yanagisawa M, Funato H, Hoshino M (2018) Forebrain Ptf1a Is Required for Sexual Differentiation of the Brain. *Cell Reports* **24**(1):79-94. doi:10.1016/j.celrep.2018.06.010

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Appendix 2　FY 2018 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, attach a “Biographical Sketch of a New Principal Investigator”(Appendix 2a).

<Results at the end of FY2018> **Principal Investigators Total: 25**

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
						e.g., a) usually stays at the center, b) stays at the center once a month, at XX satellite three times a week, and XX satellite once a year, c) joins a videoconference from another institution two times a week.	e.g., send/accept young scientists to/from the WPI center (number/period)
Center director Masashi Yanagisawa	58	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	54	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D., Neuroscience	80	April 2013	Usually stays at the center	
Hiromasa Funato	49	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba Associate Professor, Toho University	M.D., Ph.D. Neuroscience	45	December 2012	Usually stays at the center three times a week	

Robert Greene	68	Professor, Department of Psychiatry, University of Texas Southwestern Medical Center	M.D., Ph.D. Neuroscience	10	December 2013	a) visits center 3X/yr for ~2 weeks /visit b) Skype meeting with lab 1X/week c) attends (by Skype) PI meeting 1X/month d) participates in person with the annual IIIS symposium e) participates in person in annual Site Visit	Collaboration of ongoing research project at UTSW investigating role of adenosine in homeostatic sleep control
Qinghua Liu	47	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba, Japan; Investigator, National Institute of Biological Sciences (NIBS), Tsinghua University, China; Associate Professor, Center for Genetics of Host Defense, University of Texas Southwestern Medical Center, USA	Ph.D. Genetics, Molecular Biology, Biochemistry	20	April 2013	a) Stays at the center for >2 months/year; site visit, symposium b) Joins a videoconference from abroad >2 times a week c) attends (by Skype) PI meeting 1X/month	Accept young scientists to WPI center (5/period)
Hiroshi Nagase	71	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	
Makoto Satoh	63	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Sleep Medicine	75	April 2015	Usually stays at the center	
Ichiyo Matsuzaki	59	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	59	Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Endocrinology, Metabolism	15	March 2013	Usually stays at Faculty of Medicine	
Kumpei Tokuyama	65	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D., Energy Metabolims	80	April 2015	Usually stays at the center	
Akiyoshi Fukamizu	59	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	57	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	67	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	56	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	51	Professor, Department of Molecular and Cell Biology, University of California, Berkeley	Ph.D., Neurobiology	5	April 2014	Usually stays at the satellite center	
Hitoshi Okamura	66	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	56	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	52	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	49	Associate Professor International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Neuroscience	100	April 2013	Usually stays at the center	
Masanori Sakaguchi	42	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	38	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Neuroscience	100	April 2013	Usually stays at the center	
Takashi Abe	39	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	38	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	38	Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Neuroscience	100	April 2013	Usually stays at the center	

Katsuyasu Sakurai	40	Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Neuroscience	100	July 2017	Usually stays at the center	

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

Principal investigators unable to participate in project in FY 2018

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)

Katsuyasu Sakurai (40)

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

Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba

Academic degree and specialty

Ph.D. (Medical Science), Neuroscience

Effort **100** **%**

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

Research and education history

University of Tsukuba, IIIS, Tsukuba, Ibaraki, Japan

July 2017-Present

Project 1: Neural basis of innate fear induced hypothermia
Project 2: Neural representation of orgasm
Project 3: Neural basis of sleep drive

Duke University, Durham, NC, USA

- Research Associate Senior with Fan Wang — November 2013-June 2017
- Postdoctoral Fellow with Fan Wang — November 2008-October 2013

Project 1: Development of split-intein based split-Cre system
Project 2: Dissecting the organization of submodality-specific afferent input in the vibrissae column
Project 3: Generating the activity dependent neural capturing and manipulating system
Project 4: Dissecting the social fear related neural circuits

Tohoku University, Sendai, Miyagi, JAPAN

- Postdoctoral Fellow with Noriko Osumi — April 2008-October 2008
- Graduate research for Ph.D. with Noriko Osumi — April 2004-March 2008
- Ph.D., Medical Science — March 2008

Thesis: The Neurogenesis-Controlling Factor, Pax6, Inhibits Proliferation and Promotes Maturation in Murine Astrocytes

Project 1: Analyzing the role of Pax6 in astrocytes
Project 2: Generation of Pax6-floxed mouse

• Graduate research for M.S. with Yoshiaki Obara April 2002-March 2004
• M.S., Agriculture, March 2004

Project: Investigating the structural and chemical organization of goat accessory olfactory bulb

• Undergraduate study for B.S. with Yoshiaki Obara April 2001-March 2002
• B.S., Agriculture, March 2002

Project: Searching for the trigger for the onset of puberty in the goat

Achievements and highlights of past research activities

Achievements

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

a) Recipient of international awards

N/A

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 chairman of a major international academic society in the subject field

Sakurai K, Zhao S, Takatoh J, Rodriguez E, Andrew Leavitt A, Han BX, Wang F: CANE* Technology and Its Application In Dissecting the Social Fear Circuit**.** Cold Spring Harbor Laboratory Meeting. Neuronal Circuits. April, 2016 (Oral)

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)

• 「Capturing Orgasm -Understanding of sexual reward system-」 (Grant-in-Aid for Scientific Research on Innovative Areas (Will Dynamics), 2019-2020)
• 「Understanding of neural basis for mental and skin conditions affected by insufficient sleep」 (Research Grant of Koyanagi-zaidan (2018))
• 「Identification of emergency switches regulating innate fear-induced hypothermia and bradycardia」 (Grant-in-Aid for Scientific Research (C), 2018-2020)
• 「Understanding of neural basis for hypothermia regulated by TRPA1 neurons in trigeminal ganglia」 (Grant-in-Aid for Scientific Research on Innovative Areas (Thermal Biology), 2018-2019)

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

1. Rodriguez E, **Sakurai K**, Xu J, Chen Y, Toda K, Zhao S, Han BX, Ryu D, Yin H, Liedtke W,

Wang F. “A craniofacial-specific monosynaptic circuit enables heightened affective pain,” 2017, *Nature Neuroscience,* 20(12), 1734-1743. (16)

2 **Sakurai K**, Zhao S, Takatoh J, Rodriguez E, Lu J, Leavitt A, Fu M, Han BX, Wang F. “Capturing and manipulating activated neuronal ensembles with CANE delineates a hypothalamic social-fear circuit”, 2016, *Neuron*, 92(4), 739-753. (29)

3. **Sakurai K**, Akiyama M, Cai B, Scott A, Han BX, Takatoh J, Sigrist M, Arber S, Wang F. “The organization of submodality-specific touch afferent inputs in the vibrissa column”, 2013, *Cell Reports*, 5(1), 87-98. (42)

4. **Sakurai K**, Osumi N. “The neurogenesis-controlling factor, Pax6, inhibits proliferation and promotes maturation in murine astrocytes”, 2008, *The Journal of Neuroscience,* 28(18), 4604-4612. (79)

5. **Sakurai K**, Ohkura S, Matsuyama S, Katoh K, Obara Y, Okamura H. “Body growth and plasma concentrations of metabolites and metabolic hormones during the pubertal period in female Shiba goats”, 2004, *J Reprod Dev.*, 50(2), 197-205. (27)

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

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age)

Yo Oishi (38)

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

Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba

Academic degree and specialty

Ph.D. Neuroscience

Effort 100 %

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

Research and education history

Educational history:

Keio University, Japan

B.S. in Organic chemistry, Department of Applied Chemistry, Faculty of Science and Technology, 2003

M.S. in Molecular biology, Center for Biosciences and Informatics, Graduate school of Science and Technology, 2005

Osaka University, Japan

Ph.D. in Systems Neurobiology, Department of Aging Science, Graduate School of Medicine, 2009

Research history

2009-2010	Postdoctoral Associate, Department of Molecular Behavioral Biology, Osaka Bioscience Institute, Japan
2010-2013	Research Fellow, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, USA
2013-2017	Researcher, International Institute for Integrative Sleep Medicine, University of Tsukuba, Japan
2017-	Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba, Japan

Achievements and highlights of past research activities

From the graduate research to postgraduate research, Dr. Oishi have consistently focused on how the brain regulates sleep-related behaviors. Sleep–wake regulation is an excellent model for quantitatively analyzing animal behaviors to elucidate how the brain regulates the

consciousness/unconsciousness states that provide a very basic platform for the overall mental state.

While pursuing his PhD at Osaka University in Japan, Dr. Oishi joined a laboratory in Osaka Bioscience Institute (PIs: Yoshihiro Urade/Osamu Hayaishi, biochemists) to study sleep neurobiology and clarified a mechanism by which adenosine, a classic endogenous somnogen, promotes sleep. He identified a sleep-promoting mechanism of adenosine and the functional significance of adenosine deaminase in the tuberomammillary nucleus, which had not been known in the 25 years since the discovery of the adenosine deaminase localization in the tuberomammillary nucleus (Oishi et al., PNAS, 2008).

After receiving his PhD, Dr. Oishi went to Boston, MA, in the United States and spent 3 years in a laboratory at Harvard Medical School (PI: Clifford B. Saper, a neuroanatomist). He gained extensive anatomic knowledge and techniques while there, and clarified a neural mechanism underlying cataplexy, a sudden loss of muscle tone triggered by positive emotion (Oishi et al., J Neurosci, 2013). He found that chocolate produced a remarkable increase in cataplexy of narcoleptic mouse model and that the medial prefrontal cortex is a critical brain site through which positive emotions trigger cataplexy. The findings of this study provide a rough framework for elucidating the mechanisms that mediate the triggering of cataplexy by positive emotions. From a therapeutic perspective, these findings may contribute to the development of more effective and rational therapies targeting the limbic pathways that trigger cataplexy without affecting other aspects of emotion.

After returning to Japan, he joined a laboratory (PI: Michael Lazarus, a neurochemist) at the International Institute for Integrative Sleep Medicine, University of Tsukuba and clarified the sleep/wake-regulatory role of dopaminergic neurons and adenosine A2A receptors (A2AR)-expressing neurons in two motivation-related brain areas, the ventral tegmental area (VTA) and nucleus accumbens (NAc), respectively. It is currently widely accepted that sleep is regulated by two processes, homeostatic drive and a circadian process. Cognitive and emotional factors also influence sleep–wake behavior; however, the precise circuit mechanisms underlying their effects on sleep control are unknown. He found that activation of dopaminergic VTA neurons remarlably promotes wakefulness via D2/D3 receptors (Oishi et al., Brain Struct Funct, 2017). He also found that NAc A2AR-expressing neurons strongly induce SWS via ventral pallidum and the activity is regulated by motivational stimuli. These findings revealed the prominent contribution of the NAc to sleep control associated with motivation (Oishi et al., Nat Commun, 2017). In summary, his discovery of the sleep-regulatory systems involving the VTA and NAc opened a novel research field of motivation-related sleep/wake regulation.

Achievements

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

a) Recipient of international awards

N/A

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 chairman of a major international academic society in the subject field

1. Chair in The 7th IIIS Symposium, 2018, Tokyo, Japan
2. Speaker in World Sleep 2017, 2017, Prague, Czech
3. Speaker in The 5th IIIS Symposium・The 32nd Wako Workshop・Joint Meeting, 2016, Tokyo, Japan

d) Editor of an international academic journal

N/A

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

Peer review for international journals such as Sleep and Breathing or The American Journal of Drug and Alcohol Abuse.

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

Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research (B) 18H02534
2018-2023

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

1. Sleep and wakefulness are controlled by ventral medial midbrain/pons GABAergic neurons in mice (2018) *J. Neurosci.* (citation: 1)
2. Slow-wave sleep is controlled by a subset of nucleus accumbens core neurons in mice (2017) *Nat. Commun.* (citation: 24)
3. Activation of ventral tegmental area dopamine neurons produces wakefulness through dopamine D2–like receptors in mice (2017) *Brain Struct. Funct.* (citation: 29)
4. Role of the medial prefrontal cortex in cataplexy (2013) *J. Neurosci.* (citation: 58)
5. Adenosine in the tuberomammillary nucleus inhibits the histaminergic system via A1 receptors and promotes non-rapid eye movement sleep. (2008) *Proc. Nat. Acad. Sci. USA* (citation: 122)

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

Awards and fellowships:

1. Research encouragement award, Japanese Society of Sleep Research, 2018
2. Young faculty encouragement award, University of Tsukuba, 2018
3. Japan Society for the Promotion of Science Postdoctoral Fellowships for Research Abroad, 2010-2012

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age)

Kazuo Mishima (56)

Affiliation and position

Professor, Department of Neuropsychiatry, Akita University Graduate School of Medicine

Academic degree and specialty

1987 M.D. Akita University School of Medicine

1994 Ph.D. (Dr. of Medical Science), Akita University

Professional area: Psychiatry, Psychophysiology, Sleep medicine, Chronobiology

Effort 5 %

Research and education history

1987: Passed the Examination of National Board

1987-1988: Resident of Psychiatry, Akita University

1988-1991: Medical Staff in Psychiatry and Neurology, Akita-city General Hospital

1991-1994: Instructor, Department of Neuropsychiatry, Akita University

1996-2000: Assistant Professor, Department of Neuropsychiatry, Akita University

2002-2004: Research associate of Center for Biological Rhythms, Virginia University, and Visiting associate professor of Sleep Research Center, Stanford University School of Medicine

2006-2018: Director, Department of Sleep-Wake Disorders, National Institute of Mental Health, National Center of Neurology & Psychiatry

2018-present: Professor of Department of Neuropsychiatry, Akita University Graduate School of Medicine

Achievements and highlights of past research activities

Our main research topics are epidemiological surveys, development of diagnosis and treatment algorithms, and pathophysiological research on sleep-wake disorders from a clinical view point. Epidemiological surveys are conducted as part of research projects by the Ministry of Health, Labor and Welfare on sleep habit problems, prevalence of sleep-wake disorders, actual status of psychotropic drugs prescription in Japanese. In addition, we are working on development of on-line diagnostic system for sleep-wake disorders, development of treatment algorithm with improvement of cognitive / social function as a final endpoint, development of cognitive behavior therapy for insomnia and circadian rhythm sleep-wake disorders. We are also conducting basic research on pathology of hypersomnia, insomnia and circadian rhythm sleep-

wake disorders. Abnormality of biological clocks including extended circadian period, deteriorated photosensitivity, and disease susceptibility genes of circadian rhythm sleep-wake disorders are recently focused.

Achievements

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

Award-winning

2002 Encouraging prize of Japanese Society of Sleep Research

2018 54th Erwin von Bälz Prize

Japanese Society of Sleep Research (Board member)

Japanese Society for Chronobiology (Board member)

World Psychiatric Association (Board member of Sleep Wakefulness Disorders section)

World Sleep Society (International Guidelines Committee member)

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

1. Strategic Research Program for Brain Sciences (E) (2010-2014), 101,850,000yen: Molecular basis of the brain, environmental factors that supports mental and physical health throughout life: Gene-environment interaction between sleep-circadian rhythm and mental health
2. Grant-in-Aid for Scientific Research (B) (#16H05381, 2016-2018), 17,030,000yen: Elucidation of gene-environment interaction related to sleep disorders in elderly people
3. Grant-in-Aid for Scientific Research (B) (#25293255, 2016-2018), 18,070,000yen: Treatment optimization of circadian rhythm sleep disorders based on disease characteristics of biological clock
4. Health and Labour Sciences Research grants from the Japanese Ministry of Health, Labour and Welfare (#19GC1201)(2019-2020), 29,520,000yen: Research which contributes to the practice of exit strategy of psychiatric drug therapy such as appropriate continuation, tapering and cessation of psychotropic drug
5. Health and Labour Sciences Research grants from the Japanese Ministry of Health, Labour and Welfare (H29-seishin-ippan-001)(2017-2018), 24,960,000yen: Elucidation of the actual condition of prescription of psychotropic drug and research on pharmacotherapy guidelines for practicing appropriate prescription
6. Intramural Research Grant for Neurological and Psychiatric Disorders from the National Center of Neurology and Psychiatry (#29-1)(2017), 130,000,000yen: Development of a clinical pathway for sleep disorders focusing on social function/QOL improvement and exit strategy
7. Intramural Research Grant for Neurological and Psychiatric Disorders from the National Center of Neurology and Psychiatry (#26-2)(2014-2016), 43,000,000yen: Research on construction of clinical research network, operation system and resources implemented using

Platform for advanced sleep medicine (PASM)

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

1. Ayabe N, Okajima I, Nakajima S, Inoue Y, Watanabe N, Yamadera W, Uchimura N, Tachimori H, Kamei Y, Mishima K. Effectiveness of cognitive behavioral therapy for pharmacotherapy-resistant chronic insomnia: a multi-center randomized controlled trial in Japan. Sleep Med. 2018;50:105-112.
2. Tsukada E, Kitamura S, Enomoto M, Moriwaki A, Kamio Y, Asada T, Arai T, Mishima K. Prevalence of childhood obstructive sleep apnea syndrome and its role in daytime sleepiness. PLoS One. 2018;13:e0204409.
3. Okada M, Otaga M, Tsutsui T, Tachimori H, Kitamura S, Higuchi S, Mishima K. Association of sleep with emotional and behavioral problems among abused children and adolescents admitted to residential care facilities in Japan. PLoS One. 2018;13:e0198123.
4. Kishi T, Ikuta T, Matsui Y, Inada K, Matsuda Y, Mishima K, Iwata N. Effect of discontinuation v. maintenance of antipsychotic medication on relapse rates in patients with remitted/stable first-episode psychosis: a meta-analysis. Psychol Med. 2018;18:1-8.
5. Motomura Y, Kitamura S, Nakazaki K, Oba K, Katsunuma R, Terasawa Y, Hida A, Moriguchi Y, Mishima K. Recovery from Unrecognized Sleep Loss Accumulated in Daily Life Improved Mood Regulation via Prefrontal Suppression of Amygdala Activity. Front Neurol. 2017;8:306.
6. Motomura Y, Katsunuma R, Yoshimura M, Mishima K. Two Days' Sleep Debt Causes Mood Decline During Resting State Via Diminished Amygdala-Prefrontal Connectivity. Sleep. 2017;40(10).4054186.
7. Moriguchi Y, Noda T, Nakayashiki K, Takata Y, Setoyama S, Kawasaki S, Kunisato Y, Mishima K, Nakagome K, Hanakawa T. Validation of brain-derived signals in near-infrared spectroscopy through multivoxel analysis of concurrent functional magnetic resonance imaging. Hum Brain Mapp. 2017:23734.
8. Katsunuma R, Oba K, Kitamura S, Motomura Y, Terasawa Y, Nakazaki K, Hida A, Moriguchi Y, Mishima K. Unrecognized Sleep Loss Accumulated in Daily Life Can Promote Brain Hyperreactivity to Food Cue. Sleep. 2017;40(10).4085848.
9. Hida A, Ohsawa Y, Kitamura S, Nakazaki K, Ayabe N, Motomura Y, Matsui K, Kobayashi M, Usui A, Inoue Y, Kusanagi H, Kamei Y, Mishima K. Evaluation of circadian phenotypes utilizing fibroblasts from patients with circadian rhythm sleep disorders. Transl Psychiatry. 2017;7:e1106.
10. Kitamura S, Katayose Y, Nakazaki K, Motomura Y, Oba K, Katsunuma R, Terasawa Y, Enomoto M, Moriguchi Y, Hida A, Mishima K. Estimating individual optimal sleep duration and potential sleep debt. Sci Rep. 2016;6:35812.
11. Itani O, Kaneita Y, Munezawa T, Mishima K, Jike M, Nakagome S, Tokiya M, Ohida T. Nationwide epidemiological study of insomnia in Japan. Sleep Med. 2016;25:130-138.
12. Ohnishi T, Murata T, Watanabe A, Hida A, Ohba H, Iwayama Y, Mishima K, Gondo Y, Yoshikawa T. Defective craniofacial development and brain function in a mouse model for depletion of intracellular inositol synthesis. J Biol Chem. 2014;289:10785-10796.
13. BMC Neurosci. 2014;15:97.
14. Kitamura S, Hida A, Aritake S, Higuchi S, Enomoto M, Kato M, Vetter C, Roenneberg T, Mishima K. Validity of the Japanese version of the Munich ChronoType Questionnaire. Chronobiol Int. 2014;31:845-850.
15. IHida A, Kitamura S, Katayose Y, Kato M, Ono H, Kadotani H, Uchiyama M, Ebisawa T, Inoue Y, Kamei Y, Okawa M, Takahashi K, Mishima K. Screening of clock gene polymorphisms demonstrates association of a PER3 polymorphism with morningness-eveningness preference and circadian rhythm sleep disorder. Sci Rep. 2014;4:6309.

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

Appendix 3-1 FY 2018 Records of Center Activities

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

1-1. Number of researchers and other center staffs

* Fill in the number of researchers and other center staffs 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)

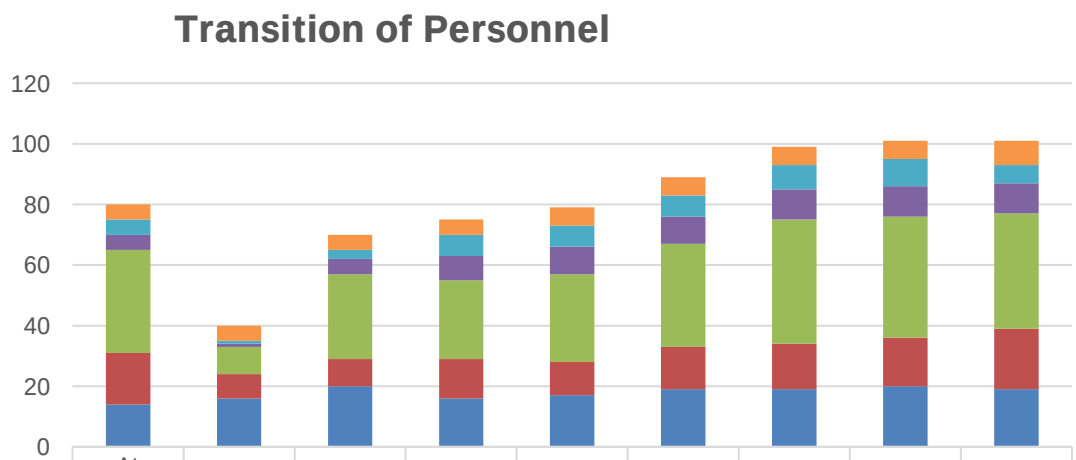
	At the beginning of project	At the end of FY 2018	Final goal (March 31, 2022)
Researchers from within the host institution	5	6	8
Researchers invited from abroad	1	9	6
Researchers invited from other Japanese institutions	1	10	10
Total principal investigators	7	25	24

b) Total members

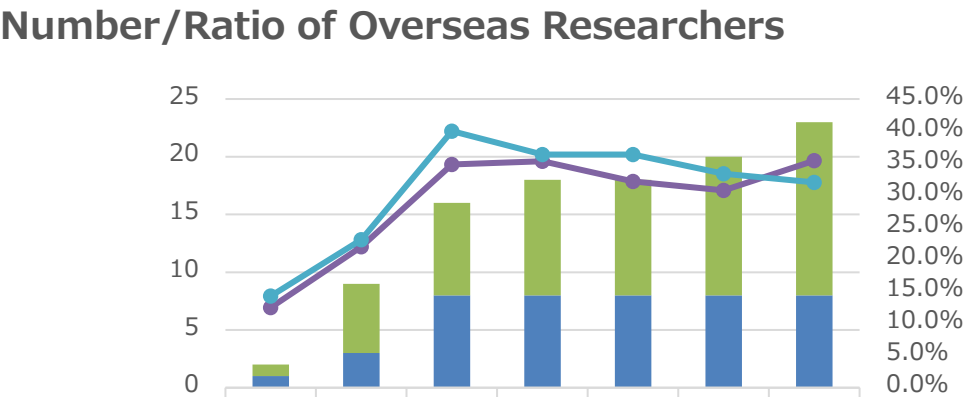
	At the beginning of project		At the end of FY2018		Final goal (March 31, 2022)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	41		65		62	
Overseas researchers	1	2	23	35.38	21	34
Female researchers	8	20	21	32.31	22	36
Principal investigators	7		25		24	
Overseas PIs	1	14	8	32	8	33
Female PIs	0	0	3	12	4	17
Other researchers	34		40		38	
Overseas researchers	0	0	15	37.5	13	34
Female researchers	8	24	18	45	18	47
Research support staffs	17		16		20	
Graduate students	4		50		68	
Administrative staffs	14		20		19	
Total number of people who form the "core" of the research center	76		151		169	

Appendix 3-2　Annual Transition in the Number of Center Personnel

*Make a graph of the annual transition in the number of center personnel since the start of project.

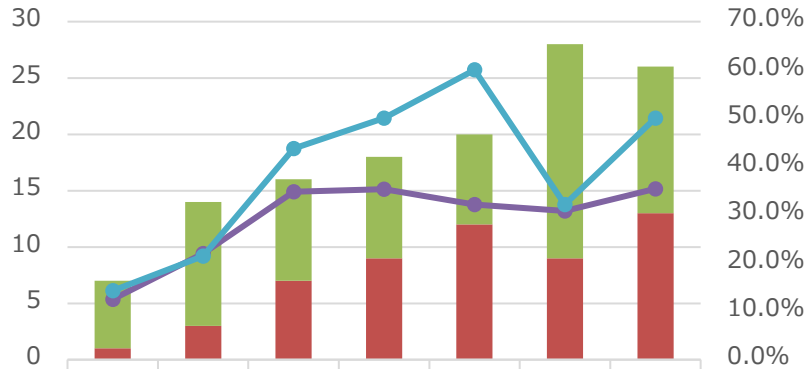


	At beginning	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Final goal
PI : Researchers from within host institution	5	5	5	5	6	6	6	6	8
PI : Researchers invited from abroad	5	1	3	7	7	7	8	9	6
PI : Researchers invited from other Japanese institutions	5	1	5	8	9	9	10	10	10
Other researchers	34	9	28	26	29	34	41	40	38
Research support staffs	17	8	9	13	11	14	15	16	20
Administrative staffs	14	16	20	16	17	19	19	20	19



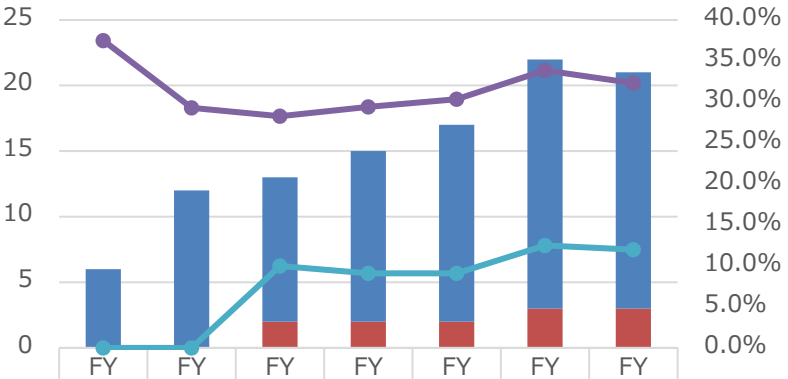
	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Other Researchers from abroad	1	6	8	10	10	12	15
PI from abroad	1	3	8	8	8	8	8
Ratio of Researchers from abroad	12.5%	22.0%	34.8%	35.3%	32.1%	30.8%	35.4%
Ratio of PIs from abroad	14.3%	23.1%	40.0%	36.4%	36.4%	33.3%	32.0%

Number/Ratio of Overseas Postdoc



	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Japanese Postdoc	6	11	9	9	8	19	13
Overseas Postdoc	1	3	7	9	12	9	13
Ratio of Researchers from abroad	12.5%	22.0%	34.8%	35.3%	32.1%	30.8%	35.4%
Ratio of Overseas Postdoc	14%	21%	44%	50%	60%	32%	50%

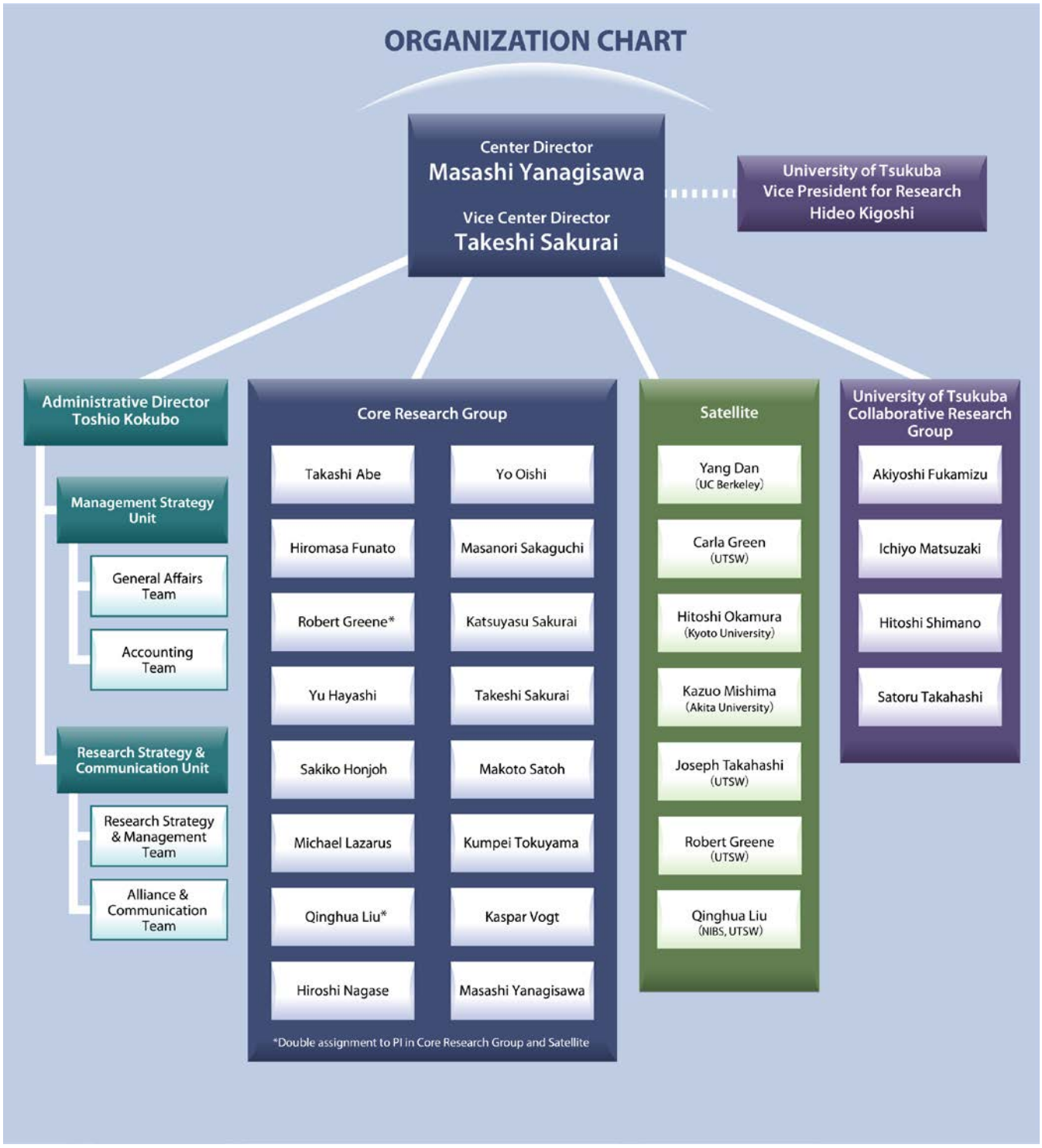
Number/Ratio of Female Researchers



	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Other Female Researchers	6	12	11	13	15	19	18
Female PI	0	0	2	2	2	3	3
Ratio of Female Researchers	37.5%	29.3%	28.3%	29.4%	30.4%	33.8%	32.3%
Ratio of Female PI	0.0%	0.0%	10.0%	9.1%	9.1%	12.5%	12.0%

Appendix 3-3 Diagram of Management System

- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any 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).



Appendix 3-4 Campus Map

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

IIIS Building

5/6F Animal Facility (ARC Satellite)

4F F-MIRAI


Nagase


Takahara

2/3F


Sakurai T.


Greene


Vogt


Lazarus


Oishi


Sakaguchi


Honjoh


Satoh


Tokuyama


Abe


Yanagisawa


Funato


Liu


Sakurai K.


Hayashi

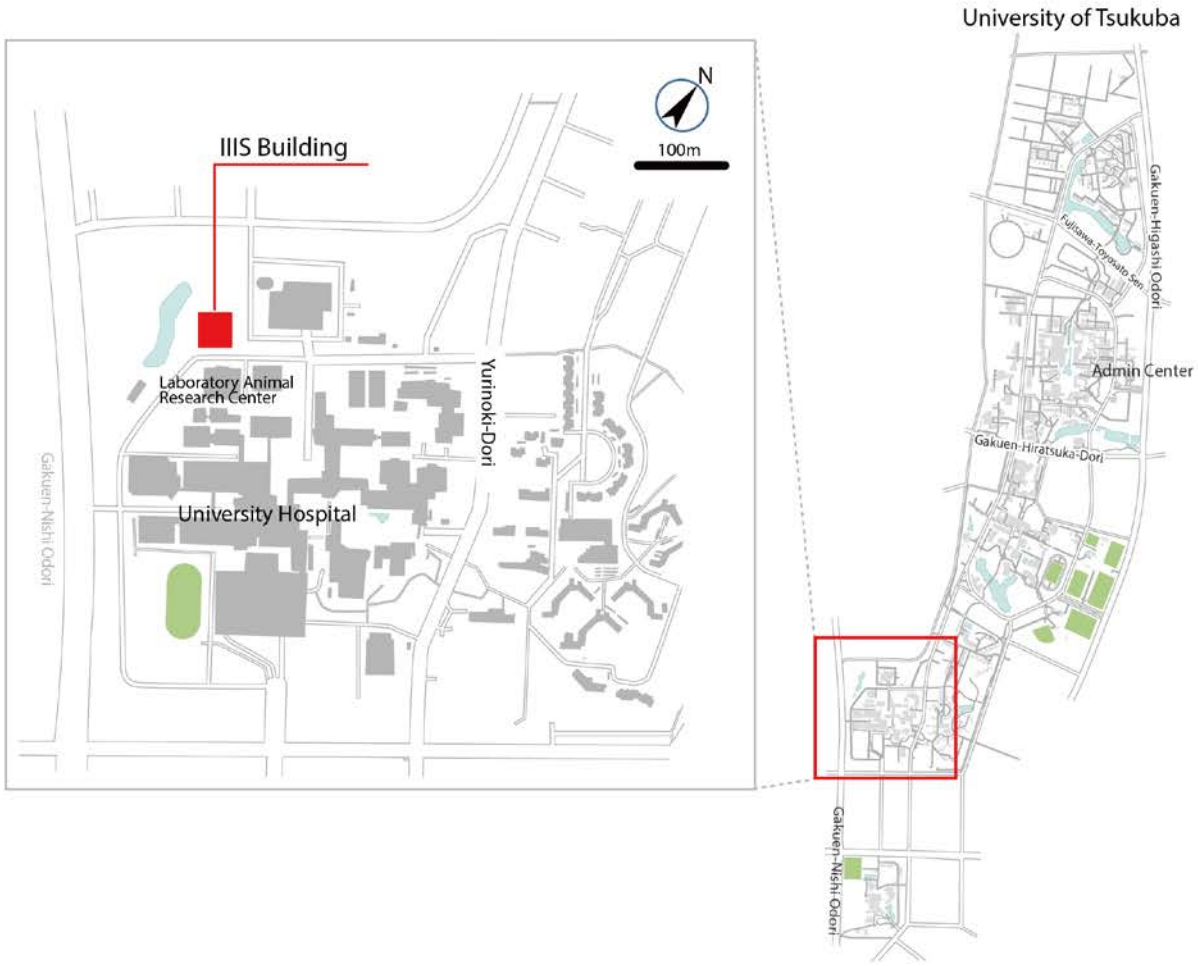
1F Admin


Kokubo

S'UIMIN


Fujiwara

Campus Map



Appendix 3-5 Project Expenditures in FY2018

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" culumn may be changed to coincide with the project’s actual content.

(Million yens)

Cost items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total costs	Amount covered by WPI funding
Personnel	Center director and administrative director	39	39
	Principal investigators (no. of persons):5	50	24
	Other researchers (no. of persons):45	294	231
	Research support staffs (no. of persons):12	39	18
	Administrative staffs (no. of persons):13	51	43
	Subtotal	473	355
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons):0	0	0
	Cost of dispatching scientists (no. of persons):0	0	0
	Research startup cost (no. of persons):17	20	20
	Cost of satellite organizations (no. of satellite organizations):2	19	19
	Cost of international symposiums (no. of symposiums):1	5	5
	Rental fees for facilities	70	59
	Cost of consumables	21	21
	Cost of utilities	88	0
	Other costs	77	77
	Subtotal	300	201
Travel	Domestic travel costs	1	1
	Overseas travel costs	3	3
	Travel and accommodations cost for invited scientists (no. of domestic scientists):0 (no. of overseas scientists):0	0	0
	Travel cost for scientists on transfer (no. of domestic scientists):1 (no. of overseas scientists):0	1	1
	Subtotal	5	5
Equipment	Depreciation of buildings	0	0
	Depreciation of equipment	771	312
	Subtotal	771	312
Research projects (Detail items must be fixed)	Project supported by other government subsidies, etc. *1		
	KAKENHI	0	0
	Commissioned research projects, etc.	155	0
	Joint research projects	90	0
	Ohers (donations, etc.)	0	0
	Subtotal	245	0
Total		1794	873

Costs (Million yens)

WPI grant in FY 2018	579
Costs of establishing and maintaining facilities	0
Establishing new facilities	0
(Number of facilities: , OO m²)	
Repairing facilities	0
(Number of facilities: , OO m²)	
Others	0
Costs of equipment procured	19
Clean Isolator	4
(Number of units:1)	
Soundproof Chamber	7
(Number of units:4)	
Others	8

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

2) Costs of satellites

(Million yens)

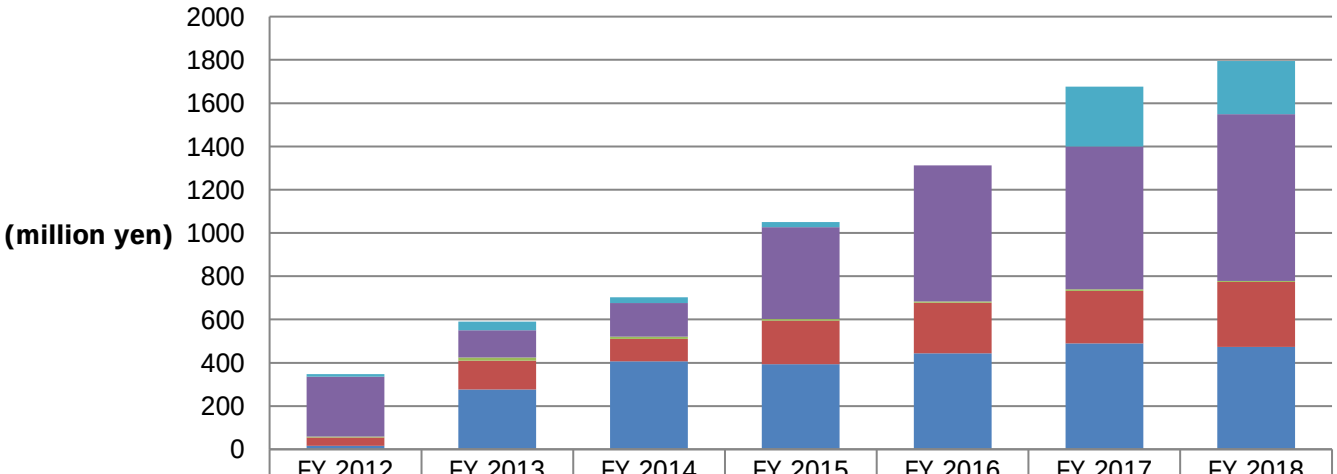
Cost items	Details	Total costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):2		
	Other researchers (no. of persons):3		
	Research support staffs (no. of persons):0		
	Administrative staffs (no. of persons):0		
	Subtotal	20	20
Project activities	Subtotal		
Travel	Subtotal		
Equipment	Subtotal		
Research projects	Subtotal		
Total		20	20

Appendix 3-6　Annual Transition in the Amounts of Project Funding

*Make a graph of the transition in the number of overall project funding.

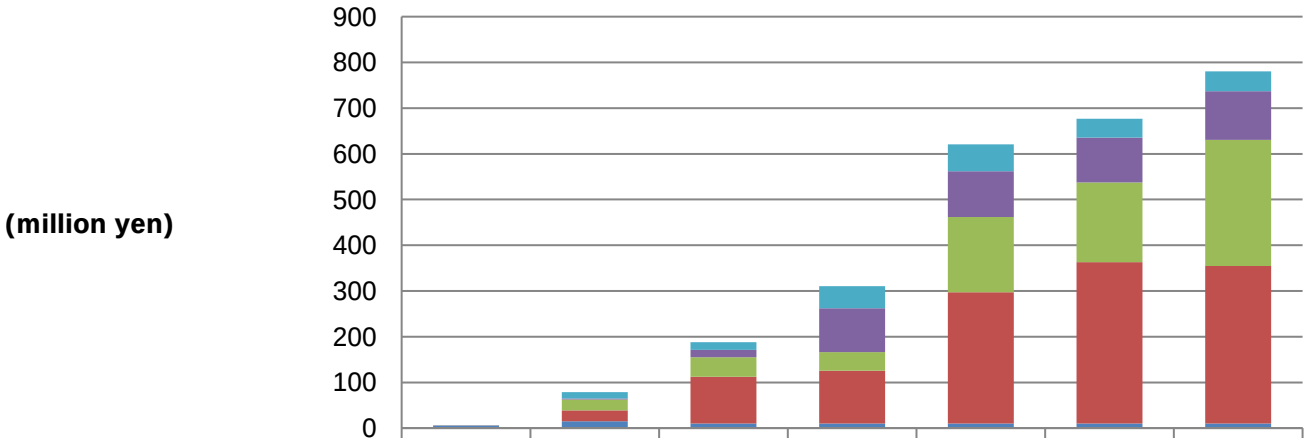
*1 Definition is as shown in Appendix 3-5 (Project Expenditures)

Transition of Project Expenditures



	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Research Projects	12	40	27	24	0	278	245
Equipment	276	125	155	425	628	659	771
Travel	4	15	10	8	6	8	5
Project Activities	39	134	105	200	235	243	300
Personnel	16	276	406	394	443	489	473

Transition of Research Project Expenditures



	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Others (donations, etc.)	1	14	17	48	59	41	43
Joint research projects	0	2	16	96	100	99	107
Commissioned research projects, etc.	0	24	43	40	165	174	276
KAKENHI	1	23	102	116	287	353	344
Project supported by other government subsidies, etc. *1	5	15	10	10	10	10	10

Appendix 4-1 FY 2018 Status of Collaboration with Overseas Satellites

- If satellite and partner institutions have been established, fill in required items of the form below.

1. Satellites and partner institutions

- List the satellite and partner institutions in the table below (including the domestic satellite institutes).
- Indicate newly added and deleted institutions in the "Notes" column.

<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	
University of California, Berkeley	Yang Dan	
Akita University Graduate School of Medicine	Tetsuo Shimizu	Retirement
Akita University Graduate School of Medicine	Kazuo Mishima	New
Ibaraki Prefecture/Ibaraki Prefectural Medical Center of Psychiatry	Takashi Kanbayashi	New
Graduate School of Pharmaceutical Sciences, Kyoto University	Hitoshi Okamura	
National Institute of Biological Sciences	Qinghua Liu	New
A global pharmaceutical company	N/A	Quit

< 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	New
The Jikei University	Megumi Shimoyama	

- If overseas satellite institutions have been established, fill in required items on the form below. If overseas satellite institutions have not been established, it is not necessary to complete the form.

2. Coauthored Papers

- List the refereed papers published in FY 2018 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 1-4. Italicize the names of authors affiliated with overseas satellite institutions.

- For reference write the Appendix 1-4 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2019 and not described in Appendix 1-4.

Overseas Satellite 1: **University of Texas Southwestern Medical Center** (Total: 4 papers)

1) Wang ZQ, Ma J, Miyoshi C, Lie YX, Sato M, Ogawa Y, Lou TT, Ma CY, Gao X, Lee C, Fujiyama T, Yang XJ, Zhou S, Hotta-Hirashima N, Klewe-Nebenius D, Ikkyu A, Kakizaki M, Kanno S, Cao LQ, Takahashi S, Peng JM, *Yu YH*, Funato H, Yanagisawa M, Liu QH (2018) Quantitative phosphoproteomic analysis of the molecular substrates of sleep need. *Nature* **558**(7710):435-439. doi:10.1038/s41586-018-0218-8

2) *Wang YB*, Cao LQ, Lee CY, Matsuo T, *Wu KJ*, Asher G, Tang LJ, Saitoh T, Russell J, Klewe-Nebenius D, *Wang L*, Soya S, Hasegawa E, Cherasse Y, *Zhou JM*, *Li YWB*, Wang T, Zhan XW, Miyoshi C, Irukayama Y, Cao J, Meeks JP, Gautron L, Wang ZQ, Sakurai K, Funato H, Sakurai T, Yanagisawa M, Nagase H, Kobayakawa R, Kobayakawa K, Beutler B, Liu QH (2018) Large-scale forward genetics screening identifies Trpa1 as a chemosensor for predator odor-evoked innate fear behaviors. *Nat. Commun.* **9**:2041. doi:10.1038/s41467-018-04324-3

3) *Bjorness TE*, Greene RW (2018) Sleep deprivation alters the time course but not magnitude of locomotor sensitization to cocaine. *Sci. Rep.* **8**:17672. doi:10.1038/s41598-018-36002-1

4) *Bjorness TE*, Greene RW (2018) Dose response of acute cocaine on sleep/waking behavior in mice. *Neurobiol. Sleep Circadian Rhythms* **5**:84-93. doi:10.1016/j.nbscr.2018.02.001

Overseas Satellite 2: University of California, Berkeley (Total: 0 papers)

None

Overseas Satellite 3: National Institute of Biological Sciences, Beijing (Total: 2 papers)

1) Wang ZQ, Ma J, Miyoshi C, Lie YX, Sato M, Ogawa Y, Lou TT, *Ma CY*, *Gao X*, Lee C, Fujiyama T, Yang XJ, *Zhou S*, Hotta-Hirashima N, Klewe-Nebenius D, Ikkyu A, Kakizaki M, Kanno S, Cao LQ, Takahashi S, Peng JM, Yu YH, Funato H, Yanagisawa M, Liu QH (2018) Quantitative phosphoproteomic analysis of the molecular substrates of sleep need. *Nature* **558**(7710):435-439. doi:10.1038/s41586-018-0218-8

2) *Wang YB*, Cao LQ, Lee CY, Matsuo T, *Wu KJ*, Asher G, Tang LJ, Saitoh T, Russell J, Klewe-Nebenius D, Wang L, Soya S, Hasegawa E, Cherasse Y, Zhou JM, Li YWB, Wang T, Zhan XW, Miyoshi C, Irukayama Y, Cao J, Meeks JP, Gautron L, Wang ZQ, Sakurai K, Funato H, Sakurai T, Yanagisawa M, Nagase H, Kobayakawa R, Kobayakawa K, Beutler B, Liu QH (2018) Large-scale forward genetics screening identifies Trpa1 as a chemosensor for predator odor-evoked innate fear behaviors. *Nat. Commun.* **9**:2041. doi:10.1038/s41467-018-04324-3

3. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2018. 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
FY2018	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

FY2018	1	3	0	0	4
	1	0	0	0	1

Overseas Satellite 2: University of California, Berkeley

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2018	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
FY2018	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
FY2018	1	0	0	0	1
	0	0	0	0	0

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2018	1	3	0	0	4
	2	0	0	0	2

Appendix 4-2　FY 2018 Visit Records of Researchers from Abroad

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

Total: 36

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
1	Qinghua Liu	47	Department of Biochemistry, University of Texas Southwestern Medical Center International Institute for Integrative Sleep Medicine University of Tsukuba National Institute of Biological Sciences, Beijing	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)	2018 May (12days) 2018 July (23 days) 2018 August (5 days) 2018 December (14 days) 2019 February (11 days)	Participation in symposium as a principal investigator, short-term stay for joint research, attend PI meetings every month and attend international meetings on behalf of IIIS
2	Robert W. Greene	68	University of Texas Southwestern Medical Center, Department of Psychiatry University of Tsukuba, International Institute for Integrative Sleep Medicine	M.D, Ph.D. Neuroscience	・Sherry Gold Knopf Crasilneck Chair in Psychiatry, in honor of Mollie and Murray Gold (2007) ・Sherry Knopf Crasilneck Distinguished Chair in Psychiatry (2004) ・Sherry Knopf Crasilneck Chair in Psychiatry, In Honor of Albert Knopf (2001-2004) ・Dept of Veterans Affairs Career Research Enhancement Award (1998) ・Swiss National Science Foundation Fellowship (Fogarty Fellowship)(1984) ・Awarded NIH T32 Training awaes for Sleep and Circadian Rhythms, Director (2018)	2018 April (14 days) 2018 October (13 days) 2018 December (5 days)	Participation in symposium as a principal investigator, short-term stay for joint research and attend PI meetings every month
3	Leon Avery		Applied Mathematics, University of Waterloo	Ph.D. Neurogenetics	・National Merit Scholarship (1973-1976) ・New York State Regents Scholarship (1973-1976) ・National Science Foundation predoctoral fellowship (1976-1979) ・Alexander von Humboldt Stiftung Fellowship (1983-1984) ・Runyon-Winchell Cancer Fund postdoctoral fellowship (1984-1987) ・NATO postdoctoral fellowship (1987-1988) ・NIH postdoctoral fellowship (1988-1990) ・March of Dimes Basil O'Connor Research Grant (1990-1992) ・NIH NHLBI Research Grant (1991-2009) ・Klingenstein Fellowship (1994-1996) ・Outstanding Teacher,University of Texas Southwestern Medical Center (1995-1996) ・Established Investigator, American Heart Association (1997-2000) ・NSF Research Grant (2001-2004) ・NIH NHLBI MERIT Award (2004-2014) ・NIH NIDDK Research Grant (2010–2014)	2018 April (2 days)	Lecture at IIIS seminar Having scientific meeting with PIs
4	Aleksandar Videnovic		Division of Sleep Medicine, Massachusetts General Hospital	M.D. Medicine Clinical Research	・School of Medicine Council Award, University of Belgrade School of Medicine(1993,1994) ・Annual Nurses Award, Northwestern Memorial Hospital Neurology Service (2003) ・Sally Marcinek Award, Northwestern Memorial Hospital (2004) ・Chairman's Award, Northwestern University Feinberg School of Medicine (2004, 2005) ・Annual Meeting Scholarship Award, American Academy of Neurology (2005) ・Chief Resident Award, Northwestern University Feinberg School of Medicine (2005) ・Dr. Susan Perlman Award, Northwestern Memorial Hospital(2005) ・Sigma Xi Research Award, Rush Graduate College (2006) ・Selected participant, Clinical Trials in Neurology Course, National Institute of Neurological Disorders and Stroke (2008) ・Selected participant, Course in Clinical and Translational Neurosciences, Selected participant, Course in Clinical and Translational Neurosciences (2009) ・Selected participant,National Institutes of Health / American Academy of Sleep Medicine (2010) ・Best Abstract Award, Parkinson Study Group Annual Symposium (2011) ・Selected member - Emerging Leaders Forum, American Academy of Neurology (2012) ・The Wayne A. Henning Sleep Medicine Investigator Award, American Academy of Neurology (2013) ・Elected Fellow AASM, American Academy of Sleep Medicine (2015) ・Elected Fellow AAN, American Academy of Neurology (2015) ・Selected participant – Leadership, Harvard Medical School (2015)	2018 May (2 days)	Lecture at IIIS seminar Having scientific meeting with Pis
5	Yulong Li	41	School of Life Sciences, Peking University	Ph.D. Neurobiology	・1000-Young-talents program, China Organization Department, Beijing (2013) ・Faculty in Neurobiology course, Marine Biological Lab, Woods Hole, MA (2007) ・The Somjen Prize for the Best Dissertation in Neurobiology, Duke University (2006) ・James Diamond Teaching Award, Duke University (2001)	2018 June (3 days)	Lecture at IIIS seminar Having scientific meeting with Pis

6	Patrick M. Fuller		Harvard Medical School, Department of Neurology, Beth Israel Deaconess Medical Center	Ph.D. Physiology Neuroscience	·NASA Achievement Award – Neurolab, STS-90 (2000) ·Achievement Reward for College Scientist, (ARCS) (2002) ·Jean McGuire Scholar, ARCS (2003) ·Phi Sigma, Delta Gamma Rho Chapter (2003) ·Jean McGuire Scholar, ARCS (2004) ·Max Klieber Award in Metabolism (2005) ·Loren D. Carlson Prize in Physiology (top PhD dissertation) (2005) ·Fellowship, NIH Training Program in Sleep, Circadian and Respiratory Neurobiology (2005) ·National Research Service Award, NIH (2007) ·NSF-SRS Young Investigator Award (2008) ·Associate Preceptor, HMS, Division of Sleep Medicine, Research Training Program (2012) ·Faculty Research Award, Department of Neurology, BIDMC (2014) ·Full Preceptor, HMS, Division of Sleep Medicine, Research Training Program (2016)	2018 June (2 days)	Lecture at IIIS seminar Having scientific meeting with Pis
7	Sandra A. Brown		Vice Chancellor for Research, University California San Diego	Ph.D. Clinical Psychology	·New Investigator Research Award, National Institute of Alcohol Abuse and Alcoholism (1983-1986) ·Graduate Faculty Research Award, Northern Illinois University (1983) ·Veterans Affairs Medical Center Outstanding Performance Awards (1986-1997) ·Department of Veterans Affairs, First Annual "Women Making a Difference Award" (1990) ·American Psychological Association, Professional Contribution Award, Division 50 (1996) ·President, Division 50-Addictions, American Psychological Association (1998-1999) ·NIAAA MERIT Investigator Award (1999-2004) ·UC San Diego Chancellor's Associates Faculty Research Excellence Award (2007) ·Top Producers of Scholarly Publications in Clinical Psychology PhD Programs (2007) ·American Psychological Association, Division 50 Society of Addiction Psychology, Distinguished Scientific Contributions Award(2013) ·Research Society on Alcoholism Marlatt Mentorship Award (2014)	2018 June (1 day)	Visit to IIIS research facilities and meeting with Director
8	Youm, Chang Hong		Department of Health Care & Science , College of Health Sciences, Dong-A University	Ph. D. Sport Biomechanics	·Dong-A University Best lecture Professor Award (2009) ·Awarded the Best Oral Presentation by the Korean Society of Athletic Training - Supported by the Student Athletic Exercise Program in the Busan Metropolitan City (2014) ·Awarded the Best Oral Presentation by the Korean Society of Kinematics (2015) ·Development of Platform for Quantifying Parkinson's Disease Analysis Process (2016) ·Health Data Validation Medical Clinical Support Project, Busan Technopark (2017) ·Validation Medical Clinical Support Project, Busan Techno Park (2018)	2018 June (1 day)	Visit to IIIS research facilities
9	Fan Wang		Department of Neurobiology, Duke University School of Medicine	Ph.D. Neurobiology	·Outstanding Student Scholarship, Tsinghua University, China (1989–1993) ·Distinguished Graduate Award, Tshinghua University, China(1993) ·Distinct Thesis Honor, Columbia University, New York (1998) ·Postdoctoral Fellowship from Howard Hughes Medical Institute (1998) ·Alfred P. Sloan Scholar (2004) ·Klingenstein Fellow in Neuroscience (2004) ·Whitehall Foundation Award (2004) ·McKnight Scholar Award (2007) ·NIH Pioneer Award (2013) ·Elected AAAS Fellow (2014) ·Brain Research Foundation SIA award (2016)	2018 July (1 day)	Lecture at IIIS seminar Having scientific meeting with Pis
10	Junghoon Kim		Department of Preventive Medicine, Gachon University College of Medicine	Ph.D. Sports Medicine	·Korean Society of Physical Education Member of the Society (2006-present) ·Member of the Korean Society for Developmental Development (2006-present) ·Current Member of the Korean Society for Obesity (2015) ·Current Member of the Korean Society of Obesity (2014-current) ·Korea exercise physiology Society member (2015- present) ·Director of Korea exercise and nutrition Sciences (2017-current) ·The Asian Journal of Kinesiology executive editor ·Director of Institute for exercise (2018- present)	2018 August (1 day)	Visitor to IIIS research facilities
11	Geonok An		Korea National University of Transportation, Sports and Health Care Major, Division of Sports	Ph.D. Clinical Exercise Medicine	·Acquired 2006 orthopedic specialist (2006) ·Army Military Medical Officer (2006-2009) ·Inje University Seoul Paik Hospital Department of Orthopedic Surgery (2009) ·Director, Sports Medicine Center, Seoul Paik Hospital, Inje University (2009)	2018 August (1 day)	Visitor to IIIS research facilities
12	Byungjoo Noh		Department of Health Care & Science / College of Health Sciences, Dong-A University	Ph.D. Sports Medicine Clinical Biomechanics	·Development of Big Data Based Run Damage Prediction System, Korea Research Foundation (Ministry of Science and Technology, Ministry of Information and Communication)(2018-2019)	2018 August (1 day)	Visitor to IIIS research facilities

13	Patrick Lévy	64	President of the University Grenoble Alpes	M.D. Medicine	・Directed the respiratory functional exploration and the sleep laboratory at Grenoble University Hospital.(1994-2019) ・Vice-President of the Company European Sleep Research Project (2009-2012) ・President of the Digital University in Health and Sport (UNESS) (2012) ・The prestigious Prix Jean-Claude Yernault Lecture, awarded by the European Respiratory Society (2015) ・Chair of the European Committee of the Conference of University Presidents (2019-2021)	2018 September (1 day)	Participation in Tsukuba Global Science Week, Visit to IIIS research facilities and meeting with Director
14	Yassine Lakhnech		University of Grenoble Alpes Executive Director, Research and Technology Transfer, Grenoble-Alpes University	Ph.D. Computer Science	・Workshop on the Link between Formal and Computational Models (2005) ・Workshop FCC'06 (Formal and Computational Cryptography); associated with ICALP'06, (2006) ・3rd Workshop FCC'07 (Formal and Computational Cryptography); associated with IEEE 20th Computer Security Foundations (2007) ・12th ASIAN Computing Science Conference Focussing on Computer and Network Security(2008) ・The Fourth Taiwanese-French Conference on Information Technology (2008) ・SafeCert 2008 International Workshop on the Certification of Safety-Critical Software Controlled Systems, (2008) ・2nd IFIP Working Conference on Verified Software: Theories, Tools, and Experiments (VSTTE 2008) ・The First International Workshop on Dependability and Security in Complex and Critical Information Systems DEPEND (2008) ・1st Canada-France MITACS Workshop on Foundations & Practice of Security(2008) ・The 6th International Workshop on Security Issues in Concurrency will be co-located with CONCUR (2008) ・Computer Aided Verification (CAV) (2009) ・Eighth ACM/IEEE International Conference on Formal Methods and Models for Codesign Grenoble, (2010) ・4th Canada-France MITACS Workshop on Foundations & Practice of Security (2011)	2018 September (1 day)	Participation in Tsukuba Global Science Week, Visit to IIIS research facilities and meeting with Director
15	Thomas E. Scammell		Beth Israel Deaconess Medical Center	M.D. Medicine	・CSB Distinguished Visiting Neuroscientist University of Toronto (2007) ・Invited Special Lecture Annual Meeting of the Associated Professional Sleep Societies (2009) ・Elected as Alumnus Member Alpha Omega Alpha (2010) ・Researcher of the Year Award Narcolepsy Network (2013) ・Sleep Science Award American Academy of Neurology (2015) ・Top Doctor 2016 Boston Magazine (2016) ・Top Doctor 2017 Boston Magazine (2017)	2018 December (2 days)	Participation in symposium as a speaker, lecture at IIIS seminar
16	Peng Cao		National Institute of Biological Sciences, Beijing	Ph.D. Neurobiology	・The Thousand Young Talents Program of China (2013-2015) ・Young PI Award, National Natural Science Foundation of China (2015-2017)	2018 December (3 days)	Participation in symposium as a speaker, lecture at IIIS seminar
17	Hee-Sup Shin	67	Center for Cognition and Sociality Institute for Basic Science Republic of Korea	Ph.D. Genetics Cell Biology	・Frank Lappin Horsfall, Jr. Award, Cornell University (1983) ・Korean Academy of Science and Technology, Member (1994) ・Kumho Science Award, Kumho Foundation (1997) ・Hantan Life Science Award, Hantan Foundation (1997) ・Award for Excellent Research Paper in Science & Technology, MOST (1998) ・Hamchun Medical Science Award, Hamchun Foundation (2000) ・Person of the Month, KIST (2003) ・Scientist-of-the-month Award, MOST (2004) ・Dupont Prize, Dupont Foundation (2004) ・Grand Prize, KIST (2004) ・Hoam Prize, Hoam Foundation (2004) ・Order of Civil Merit (Dongbaeg Medal), President of Korea (2004) ・AHF Lectureship Award, Calgary University, Canada (2004) ・Best Scientist Award, MOST, Korea (2005) ・National Honor Scientist, MOST, Korea (2006) ・National Academy of Science, USA, Foreign Associate (2009) ・Frank Lappin Horsfall, Jr. Award, Cornell University Graduate School of Medical Science (1983) ・Korean Academy of Science and Technology, Member (1994) ・Kumho Science Award, Kumho Foundation (1997) ・Hantan Life Science Award, Hantan Foundation (1997) ・Award for Excellent Research Paper in Science & Technology, MOST (1998) ・Hamchun Medical Science Award, Hamchun Foundation (2000) ・Person of the Month, KIST (2003) ・Scientist-of-the-month Award, MOST (2004) ・Dupont Prize, Dupont Foundation (2004) ・Grand Prize, KIST (2004) ・Hoam Prize, Hoam Foundation (2004) ・Order of Civil Merit (Dongbaeg Medal), President of Korea (2004) ・AHF Lectureship Award, Calgary University, Canada (2004) ・Best Scientist Award, MOST, Korea (2005) ・National Honor Scientist, MOST, Korea (2006) ・National Academy of Science, USA, Foreign Associate (2009)	2018 December (1 day)	Participation in symposium as a speaker
18	Pierre J. Magistretti		Division of Biological and Environmental Sciences and Engineering, KAUST, Thuwal, Saudi Arabia Brain Mind Institute, EPFL, Lausanne, Switzerland Department of Psychiatry UNIL/CHUV, Switzerland	M.D, Ph.D. Neuroscience	・Recipient of the Theodore-Ott Prize of the Swiss Academy of Medical Sciences (1997) ・Elected Member of Academia Europaea (2001) ・Elected Member of the Swiss Academy of Medical Sciences, ad personam (2001) ・Recipient of the Emil Kraepelin Guest Professorship, Max Planck Institute für Psychiatry, Münich (2002) ・Elected Professor at Collège de France, Paris, International Chair (2007-2008) ・Goethe Award for Psychoanalytic Scholarship, Canadian Psychological Association (2009) ・Camillo Golgi Medal Award, Golgi Fondation (2011) ・Elected Member of the American College of Neuro Psychopharmacology (ACNP)(2011)	2018 December (1 day)	Participation in symposium as a speaker

19	Takao Hensch		Conte Center at Harvard Molecular and Cellular Biology, Harvard University Neurology, Boston Children's Hospital, Harvard Medical School International Research Center for Neurointelligence, The University of Tokyo	Ph.D. Neuroscience	・Thomas T. Hoopes Prize, Harvard (1988) ・JW Fulbright Fellowship (1990) ・MEXT Research Scholarship (1988-1991) ・Tsukahara Prize, Japan Brain Science Foundation (2001) ・NISTEP award (2005) ・U.S. Society for Neuroscience Young Investigator Award (2005) ・MEXT Minister's Prize (2006) ・NIH Director's Pioneer Award (2007) ・Mortimer D Sackler Prize (2016)	2018 December (1 day)	Participation in symposium as a speaker
20	Milan Kumar Sanyal	65	Surface Physics and Materials Science Division, Saha Institute of Nuclear Physics	Ph.D. Physics	・First prize in the Fifth Colloquium for Young Physicists (1987) Indian Physical Society. ・N.S. Satya Murthy memorial Young Scientist award of the Indian Physics Association (1987) ・Medal of Material Research Society, India (2000) ・ Fellow, Indian National Science Academy (2001) ・Fellow, Indian Academy of Sciences (2002) ・Fellow, The National Academy of Sciences, India (2003). ・J.C. Bose National Fellowship (2007–2022) ・DAE Raja Ramanna Lecture in Physics (2008) ・Member, Indian National Science Academy Council (2010-2013) ・Member, Science Advisory Committee of the Cabinet, Government of India (2009-2015) ・CNR Rao Prize Lecture in Advanced Materials (2013) ・President, Indian Physical Society (2009-2013) ・President, Indian Physics Associations (2010-2013) ・Fellow, The World Academy of Science (2016) ・National Research Award, Nano Science and Technology, Government of India (2017) ・Raja Ramanna Fellowship (2018–Present)	2019 February (1 day)	Visitor to IIIS research facilities and meeting with Director
21	M. Lakshmi Kantam	64	Department of Chemical Engineering, Institute of Chemical Technology, Mumbai	Ph.D. Chemistry	・Chairperson, Subject Expert Committee, Women Scientists Scheme, Department of Science and Technology, Government of India. ・Member, Board of Studies, Andhra University, Visakhapatnam. ・Editorial Board Member, Chemical Record (TCR), Wiley-VCH. ・+A1Editorial Board Member, Journal of Chemical Sciences, Springer Publishers ・ Fellow of Andhra Pradesh Akademy of Sciences, Hyderabad (2006) ・ RMIT Foundation Fellowship Award, RMIT Uni, Australia (2007) ・ B.D.Tilak Visiting Fellow,UICT, Mumbai (2008) ・Adjunct Professor, RMIT University, Melbourne, Australia (2008) ・Fellow of National Academy of Sciences, India (2008) ・Lifetime Achievement Award, Indian Chemical Society (2011) ・ Vasvik Award (2011) ・ Fellow of The Royal Society of Chemistry, UK (2013) ・Fellow of the Indian National Science Academy (2014) ・Eminent Scientist Award –Catalysis Society of India (2015)	2019 February (1 day)	Visitor to IIIS research facilities and meeting with Director

					·National Talent Test Award (1975-1978) ·Calicut University Merit Scholarship (1983-1985) ·Indo-US Science and Technology Fellowship (1992-1993) ·Rajiv Gandhi Award for Innovative ideas in Science and Technology (1995) ·Tamilnadu Scientist Award (2000) ·Materials Research Society of India Medal (2002) ·Young Scientist Award, Chemical Research Society of India (2003) ·Swarnajayanti Fellowship (Project) of the DST Chemical Research Society of India Medal (2004) ·Fellow, Madras Science Foundation (2005) ·Editorial board member of two journals in chemistry ·National Research Award in Nano Science and Technology by the Department of Science and Technology, Government of India (2008) ·Shanti Swaroop Bhatnagar Prize in chemical sciences (2008) ·Elected fellow of the Indian Academy of Sciences (2009) ·Kerala Sahitya Academy Award for Knowledge Literature (2010) ·Professor S. S. Deshpande National Award (2011) ·Editorial Board Member of the journal, ACS Applied Materials and Interfaces (2012) ·International Editorial Advisory Board Member of the journal, Surface Innovations (2012) ·India Nanotech Innovation Award (2012) ·Elected fellow of the Indian National Academy of Engineering (2014) ·Fellow of the Royal Society of Chemistry, FRSC (2014-) ·Lifetime Achievement Research Award of IIT Madras (2015) ·Member, Editorial Board of the journal, Scientific Reports (Nature Group) (2015-) ·Elected fellow of the Indian National Science Academy (2016) ·Elected fellow of The National Academy of Sciences (2015) ·Member, Editorial board of International Journal of Water and Wastewater Treatment (2015) ·Member, Editorial Advisory Board of the journal, Chemistry of Materials, (2018-) ·Member, Editorial Advisory Board of the journal, ACS Nano (2018-) ·IITM Alumni Association Award for Faculty in Innovation (2018) ·The World Academy of Sciences (TWAS) Prize in Chemistry (2018) ·Elected Fellow of the American Association for the Advancement of Science (AAAS)(2018-) ·Elected Fellow of The World Academy of Sciences (TWAS), 2019- ·Member, Advisory Board of the new RSC journal, Nanoscale Advances ·Member, Governing Council, Technology Information, Forecasting & Assessment Council (TIFAC) ·Member, Research Advisory Council, Manipal Academy of Higher Education, Manipal ·Member, Research Advisory Board (RAB), Pandit Deendayal Petroleum University		
22	T. Pradeep	55	Department of Chemistry Indian Institute of Technology Madras	Ph.D. Molecular materials		2019 February (1 day)	Visitor to IIIS research facilities and meeting with Director
23	V. Nagaraja	64	Department of Microbiology and Cell Biology, Indian Institute of Science	Ph.D. Cell Biology	·Shanti SwarupBhatnagar Award (1999) ·Srinivasaya Memorial Award (2001) ·First Product Process and Technology Development Award of DBT(2001) ·Ranbaxy Science Foundation Award (2003) ·J. C. Bose Fellowship (2008) ·Dr.NityaAnanad Endowment Lecture Award of INSA (2009) ·J. C. Bose Medal of Indian National Science Academy (2010) ·TWAS Prize in Biology (2011)	2019 February (1 day)	Visitor to IIIS research facilities and meeting with Director

24	Harinder P. Singh		Department of Physics & Astrophysics, University of Delhi	Ph.D. Physics	·Guest Observer, Loiano Observatory, Italy (2000) ·Guest Observer, INAOE observatory, Hermisillo, Mexico, (2000) ·Guest Observer, Mt. Wilson Observatory (Caltech), Califiornia, USA (2000) ·Councilor, Astronomical Society of India (2007-2009) ·Member, Users Committee, IUCAA, Pune (2007-2009) ·Guest Observer, Kitt Peak National Observatory, Tucson, Arizona, (2000-2003) ·Visiting Professor, Yonsei University, Seoul, South Korea (2009-2010) ·Invited Professor, Lyon Observatory, Claude Bernard University, France (2008, 2009, 2011, 2012, 2018) ·Visiting Professor, University of Stuttgart and MPI for Astrophysics Heidelberg, Germany (2007), Uni.-Marburg (2015, 2017) ·Visiting Faculty, State University of New York at Oswego (2014, 2015, 2016) ·Visiting Faculty, University of North Carolina at Chapel Hill, USA (2000, 2002); Aspen Center for Physics (2015) ·Visiting Faculty, University of North Carolina at Chapel Hill, USA (2000, 2002); Aspen Center for Physics (2015) ·Visiting Faculty, Queen Mary University of London (1999, 2000) ·Visiting Faculty, Hong Kong University of Science & Technology (1995, 1997, 2001, 2015) ·Member, Planning & Programming Committee, National Science Centre, New Delhi (2012-14)·Member, Editorial Board, Bulletin of Astronomical Society of India (2010-2016) ·Member, Planning & Programming Committee, National Science Centre, New Delhi (2012-14) ·Vice President, Astronomical Society of India (2013-16) ·Member, Governing Council, IUCAA (2012-14) ·Dean (Examinations) University of Delhi (2012) ·Proctor, University of Delhi (2010-2012 ·Director, Centre for Science Education & Communication, University of Delhi (2010-2012)	2019 February (1 day)	Visitor to IIIS research facilities and meeting with Director
25	Bimal K. Roy		Head, Cryptology Research Group Indian Statistical Institute	Ph.D. Combinatorics	·IBM Faculty Award for research, teaching and initiative in Cryptology (2007) ·Reliance Platinum Jubilee Award, National Academy of Science, India (2007) ·Fellow, National Academy of Sciences, India (2010-) ·Fellow, Indian Society for Probability and Statistics (2014) ·Teacher' s Award, Indian National Science Academy (2014) ·Padma Shri Award, Government of India (2015)	2019 February (1 day)	Visitor to IIIS research facilities and meeting with Director
26	Lee-Wei Yang	43	Inst. of Bioinformatics and Structural Biology, National Tsing Hua University	Ph.D. Molecular Genetics and Biochemistry	·JSPS Visiting Fellow, Kinki University, Osaka, Japan 2005 ; Tokyo University (2015, 2016, 2017)	2019 March (1 day)	Visitor to IIIS research facilities and participation in TARA International Symposium as a speaker

27	Michelle Tallquist		Center for Cardiovascular Research, John A. Burns School of Medicine, University of Hawai	Ph.D. Molecular Biology	・Associate Professor, University of Texas Southwestern Medical Center (2009-2011) ・Assistant Professor, University of Texas Southwestern Medical Center (2001-2009)	2019 March (1 day)	Visitor to IIIS research facilities and participation in TARA International Symposium as a speaker
28	Zhi-Ping Liu		Internal Medicine - Cardiology Molecular Biology, UT Southwestern Medical Center	Ph.D. Biophysics	・University of Science and Technology of China, Computer Science(1982) ・Shanghai Institute of Biochemistry (1986) ・UT Southwestern Medical Center(1993)	2019 March (1 day)	Visitor to IIIS research facilities and participation in TARA International Symposium as a speaker
29	Hong-Gang Wang		Pediatrics and Pharmacology, Division of Hematology and Oncology, Penn State College of Medicine	Ph.D. Biophysics	・Mechanisms of Rad9 Mediated Checkpoints and Apoptosis (2002-2008) ・Targeting of MDM2 Family Proteins in Cancer (2006-2013) ・Regulation of Autophagy and Tumorigenesis by Bif-1 (2009-2015) ・Non-canonical Caspase-8 Activation on Autophagosomal Membranes (2018) ・Autophagosome closure by the ESCRT machinery (2018)	2019 March (1 day)	Visitor to IIIS research facilities and participation in TARA International Symposium as a speaker
30	Bernd K. Fleischmann		Institute of Physiology I, Medical Faculty, University of Bonn	M.D. Medicine	・Habilitation award of the Medical Faculty, University of Cologne (2000) ・Director and Chair, Institute of Physiology I, Medical Faculty, University of Bonn (2003) ・Speaker of the Cardiovascular Research Area, Medical Faculty, University of Bonn (2005-2018) ・Adjunct Professor, Xi'an Jiatong University, Xi'an, China (2007-2010) ・Vice-Dean of Finances of the Medical Faculty, University of Bonn, Germany (2008) ・Member of the Program Committee of the German Society of Cardiology (2011-2015) ・Member of the Senate of the German Research Foundation (DFG) (2013) ・Visiting Professor (Sigma), Tsukuba University, Tsukuba, Japan (2014) ・Member of the German Research Council Committee "Animal Research" (2014) ・Member of the German Research Council Committee "Fundamental Questions in Clinical Research" (2016) ・Member of the German Research Council Committee "Scientific Misconduct" (2017) ・Member of the National Academy of Sciences "Leopoldina" (2017)	2019 March (1 day)	Visitor to IIIS research facilities and participation in Symposium for the Ph.D Program in Humanics as a speaker
31	Ian Chambers		MRC Centre for Regenerative Medicine, School of Biological Sciences, University of Edinburgh	Ph.D. Biochemistry	・Elected Member of the European Molecular Biology Organisation, EMBO (2014) ・Elected Fellow of the Royal Society of Biology (2015) ・Elected Fellow of the Royal Society of Edinburgh (2015) ・Visiting Professor, University of Tsukuba (2018-present)	2019 March (1 day)	Visitor to IIIS research facilities and participation in Symposium for the Ph.D Program in Humanics as a speaker
32	Seong-Jin Kim		Precision Medicine Research Center, Advanced Institutes of Convergence Technology, Seoul National University	Ph.D. Medical Science	・Ho-Am Prize in Medicine (2002) ・Dongkok Prize (2011) ・Gold Ribbon Lecture (2015) ・Japan Cancer Association International Award (2017)	2019 March (1 day)	Visitor to IIIS research facilities and participation in Symposium for the Ph.D Program in Humanics as a speaker
33	Tilo Kunath		MRC Centre for Regenerative Medicine, School of Biological Sciences University of Edinburgh	Ph.D. Developmental Biology	・MRC Neurosciences and Mental Health Project Grant (2012–2015) ・Parkinson's UK Senior Fellowship extension (2013– 2016) ・MRC Regenerative Medicine Research Committee Project Grant (2013– 2016) ・UCB BioPharma Industrial Contract (2016-2019) ・Wellcome Trust Clinical PhD Fellowship (2016-2019) ・Cure Parkinson's Trust Project Grant (2016-2019) ・R S Macdonald Trust Awards Grant for Further Stem Cell Research (2018)	2019 March (1 day)	Visitor to IIIS research facilities and participation in Symposium for the Ph.D Program in Humanics as a speaker
34	Kerry Dixon		Executive Director of Community and Global Engagement, College of Education and Human Ecology, The Ohio State University	Ph.D. Interdisiplinary Teaching and Learning	・Jeffrey P.Charde Outstanding Senior Award (1987-1991) ・Research Lead: Innovative Curriculum Design Team, Project ASPIRE (2009-2015) ・Arts Integration Instructional Coach (2007-2013)	2019 March (1 day)	Visitor to IIIS research facilities and meeting with Director
35	Donald Pope-Davis		Dean, College of Education and Human Ecology, The Ohio State University Stanford University	Ph.D. Counseling Psychology	・Fellow, Division of the Psychological Study of Ethnic Minority Issues (1999) ・Fellow, Division of Counseling Psychology (2002) ・Fellow, Kroc Peace Studies Institute, University of Notre Dame (2002-2013) ・Fellow, Center for Social Concerns (2003-2008) ・Fellow, Alliance for Catholic Education (2003-2013) ・Director of the Multicultural Research Institute (MRI) at the University of Notre Dame (2002-2008) ・American Psychological Association Ranked 3rd in the country as a leading contributor/impact in the multicultural counseling literature, (Journal of Counseling Psychology (2007) ・Dean of the College of Education at New Mexico State University ・Elected fellow of the American Psychological Association's Society ・Fellow of the Society of Counseling Psychology. New Mexico State ・Kellogg Foundation grant ・NAACP of New Mexico's Distinguished Keynote Award ・Benedictine University's Leadership Innovation Philanthropy Award ・University of Notre Dame's Hesburgh Diversity Lecture Award ・Contributed National Black Catholic Survey (2011) ・Hesburgh Distinguished Diversity Lecture Award University of Notre Dame (2012)	2019 March (1 day)	Visitor to IIIS research facilities and meeting with Director

36	Xiaoliang Zhao		Neurology, Mayo Clinic	Ph. D. Neurobiology	・Outstanding Undergraduates Scholarship, First Class, Department of Life Sciences, Sichuan University (2004) ・Scholarship for Excellent Ph.D. Student, Institute of Neuroscience, CAS (2006/2009) ・Pfizer Scholarship of Life Science, 1st class, Shanghai Institute for Biological Sciences, CAS (2010)	2019 March (3 days)	Lecture at IIIS seminar Having scientific meeting with PIs

Appendix4-3 Postdoctoral Positions through Open International Solicitations

* In the column of number of applications and number of selection, put the total number (upper), the number and percentage of overseas researchers in the < > brackets (lower).

Fiscal year	number of applications	number of selection
FY2012	3	3
	< 1,33 %>	< 1,33 %>
FY2013	169	12
	<158 ,93 %>	< 4, 33%>
FY2014	144	9
	<123 , 85%>	< 3, 33%>
FY2015	98	4
	< 97, 99%>	< 3,75 %>
FY2016	29	0
	< 29, 100%>	< 0, 0%>
FY2017	45	4
	< 45, 100%>	< 2, 50%>
FY2018	33	4
	< 13, 39%>	< 4, 100%>

Appendix4-4 Status of Employment of Postdoctoral Researchers

* Prepare the information below during the period from the start of the center through March 2019.

* List each researcher in 1 line. If the list exceeds this form, add extra pages.

Japanese Postdocs

Period of project participation	Previous affiliation, position title (Country)	Next affiliation, position title (Country)
Apr 1, 201~Nov 30, 2013	Greensogna, Inc. Chief Researcher (Japan)	Tsukuba Primate Research Center, National Institutes of Biomedical Innovation, Health and Nutrition, Researcher (Japan)
Jul 1, 2013~Jun 30, 2014	University of Texas Southwestern Medical Center , Assistant Professor (USA)	The University of Tokyo, Assistant Professor (Japan)
Apr 1, 2014~Mar 31, 2015	Molecular Mechanism and Control of Complex Behaviors, University of Tsukuba, Researcher (Japan)	Japan Society for the Promotion of Science, Research Fellowship for Young Scientists (Japan)
Apr 1, 2014~Mar 31, 2017	Molecular Mechanism and Control of Complex Behaviors, University of Tsukuba, Researcher (Japan)	Japan Society for the Promotion of Science, Research Fellowship for Young Scientists (Japan)
Apr 1, 2015~Mar 31, 2017	Faculty of Health and Sport Sciences, University of Tsukuba , Researcher (Japan)	Institute of Neurology Research, Researcher (Japan)
Jun 16, 2014~May 31, 2017	University of Texas Southwestern Medical Center, Postdoctoral Researcher (USA)	Neurospace Corporation, Director CTO (Japan)
Oct 1, 2013~Dec 31, 2017	Osaka Bioscience Institute, Special Project Researcher (Japan)	The University of Tokyo, Researcher (Japan)
Apr 1, 2014~Mar 31, 2018	Molecular Mechanism and Control of Complex Behaviors, University of Tsukuba, Researcher (Japan)	National Agriculture and Food Research Organization , Researcher (Japan)
Apr 1, 2014~Mar 31, 2018	Molecular Mechanism and Control of Complex Behaviors, University of Tsukuba, Researcher(Japan)	Department of Life Scitence, Imperial College London, Visiting Researcher (UK)
Apr 1, 2017~Mar 31, 2018	Graduate School of Medical and Pharmaceutical Sciences , Chiba University , Student(Japan)	Graduate School of Life Dentistry at Niigata, Nippon Dental University, Student (Japan)
Feb 1, 2017~May 31,2018	National Museum of Emerging Science and Innovation , Science Communicators (Japan)	S'UIMIN Inc., Busuness Strategy and Development Leader (Japan)
Apr 1, 2017~Sep 30, 2018	Keio University, Doctoral course student (Japan)	NARD institute Ltd., Researcher (Japan)
Apr 1, 2018~Dec 19, 2018	University of Tsukuba , Ph.D. Program student (Japan)	Massachusetts Institute of Technology, Postdoctoral Fellow (USA)
Sep 1, 2017~Mar 31, 2019	Kyoto University, Reseacher (Japan)	Japan Society for the Promotion of Science, Research Fellowship for Young Scientists, researcher (Japan)
Apr 1, 2018~Mar 31, 2019	Keio University, Doctoral course student (Japan)	Chuo University, Assistant Professor (Japan)

Overseas Postdocs

Period of project participation	Previous affiliation, position title (Country)	Next affiliation, position title (Country)	Nationality
Apr 1, 2013~Dec 31, 2013	Osaka Bioscience Institute, Special Project Researcher (Japan)	Department of Pharmacology and Toiology, Indiana University School of Medicine South Bend, Post-doctoral Researcher (USA)	India
Jul 28, 2014~Nov 27, 2016	Department of Psychology, MacEwan University, Lecturer (Canada)	Wasda University, Assistant Professor (Japan)	Canada
Sep 16, 2014~Sep 30, 2015	Max Planck Institute of Psychiatry, Postdoc (Germany)	Japan Society for the Promotion of Science, Postdoctoral Fellowships for Research, Researcher（Japan)	India
Mar 1, 2014~Mar 31, 2017	Friedrich Miescher Institute for Biomedical Research, Postdoc (Swiss)	University of Tsukuba, Faculty of Health and Sport Sciences, Reseacher (Japan)	Canada
Apr 1, 2015~Mar 31, 2017	School of Integrative and Global Majors, University of Tsukuba, Assistant Professor (Japan)	University of Tsukuba, Graduate School of Pure and Applied Sciences, Researcher (Japan)	UK
Apr 23, 2015~Apr 23, 2016	Strasbourg University, PhD (France)	Harvard Medical School, Harvard University, Reseacher (USA)	Morocco
Jan 11, 2017~Jan 10, 2018	Department of Biological Sciences and Bioengineering, Indian Institute of Technology Kanpur, Postdoctoral Fellow (India)	Southwest University, Reseacher (China)	India
Jan 1, 2018~Mar 31, 2018	Leiden University Medical Center, Research Fellow (Nederland)	Japan Society for the Promotion of Science, Postdoctoral Fellowships for Research, Reseacher (Japan)	France

Appendix4-5 List of the Cooperative Research Agreements with Overseas Institutions

*Prepare the information below during the period from the beginning of the Center through March 2019.

1. Name of an Agreement : Collaboration Research Agreement and Sponsored Research agreement
   Dates of an Agreement : From November, 2013 through March 31, 2022
   Counterpart of an Agreement : University of Texas Southwestern Medical Center (UTSW)
   Summary of an Agreement : The UTSW has been the research center of Institute Director, Masashi Yanagisawa, for more than 20 years and has nurtured a close relationship as an IIIS satellite. The four satellite PIs (J. Takahashi, R. Greene, C. Green and Q. Liu) and joint research with the respective satellite PIs has been conducted since establishing IIIS, as well as concluding joint research or sponsored research agreements when research funds were provided. Liu engaged in research into intracellular signal transduction of sleep control nerve cells by analyzing phosphoprotein using mass spectrometric techniques and joint research into the molecular control mechanism of essential terror by forward genetics using an ENU mutant mouse and serves as Professor at the University of Tsukuba and associate professor at UTSW as a joint appointment (35:65) between both universities and intellectual property rights belonging to both universities based on this joint appointment. C. Green engaged in sponsored research into RNA analysis of sleep-deprived mice, R. Greene covered sponsored research on sleep homeostasis and the sleep-awakening control of adenosine, and Takahashi covered sponsored research on rhythm control of sleep. To further enhance Institute Director, Yanagisawa, concurrently serves as Professor at the University of Tsukuba and UTSW as a joint appointment (95:5) between both universities and intellectual property rights belonging to the Institute Director go to both universities based on this joint appointment.

2. Name of an Agreement : Collaborative Research Agreement
   Dates of an Agreement : N/A
   Counterpart of an Agreement : A global pharmaceutical company
   Summary of an Agreement : N/A

3. Name of an Agreement: Joint Research Agreement
   Dates of an Agreement: From April 1, 2017 through March 31, 2022
   Counterpart of an Agreement: Gui de Chauliac Hospital
   Summary of an Agreement: We have started a joint research with Sleep Disorder Centre, Neurology Department, Gui de Chauliac Hospital with the purpose of discovery of human genetic factor of sleep disorder entitled of investigation of human genetic factor using biobank of sleep disorder patients. IIIS will perform exome and whole genome sequences of DNA extracted from the clinical sample from sleep disorder patients such as narcolepsy and idiopathic hypersomnia at Sleep Disorder Centre.

4. Name of an Agreement: Collaboration Research Agreement
   Dates of an Agreement: From January 1, 2019 through March 31, 2022
   Counterpart of an Agreement: University of Texas Southwestern Medical Center (UTSW) and National Institute of Biological Sciences (NIBS)
   Summary of an Agreement: The PI, Q. Liu had been jointly appointed between UTSW and University of Tsukuba. From January 2019, he is jointly employed by three organization of NIBS, UTSW, and Tsukuba, and UT Southwestern and is engaged in research to conduct innate fear screens to identify and characterize fear mutant mice and conduct sleep studies to elucidate mechanisms of sleep/wake regulation. He serves as Investigator at NIBS, Associate Professor at UTSW, and professor at the University of Tsukuba as a joint appointment (55:25:30) among three universities. His primary research commitment is to his laboratory at NIBS.

5. Name of an Agreement: Joint Research Agreement
   Dates of an Agreement: From January 1, 2019 through December 31, 2019
   Counterpart of an Agreement: Wenzhou Medical University
   Summary of an Agreement: We have started a joint research with Wenzhou Medical University entitled of Identifying negative allosteric negative modulators of adenosine A_{2A} receptor. We will use the mA_{2A}R-CHO cells to screen low-molecular-weight compounds (synthesized at IIIS) for

allosteric effects at $A_{2A}R$ and Wenzhou Medical University send a postdoctoral fellow with the experience in adenosine receptor biology and neuroscience to work at IIIS.

Appendix4-6 Holding International Research Meetings

* Indicate up to ten of most representative international research conferences or symposiums held from the start of the center through March 2019 and give the number of participants using the table below.

Date	Meeting title and Place held	Number of participants
Dec 20, 2018	Title: The 7th Annual IIIS Symposium Venue: Tokyo Conference Center Shinagawa	From domestic institutions: 201 From overseas institutions: 13
Dec 14, 2017	Title: The 6th Annual IIIS Symposium Venue: Tokyo Conference Center Shinagawa	From domestic institutions: 185 From overseas institutions: 11
Dec 12, 2016	Title: The 5th Annual IIIS Symposium Venue: Tokyo Conference Center Shinagawa	From domestic institutions: 170 From overseas institutions: 7
Feb 26, 2016	Title: The 4th Annual IIIS Symposium Venue: IIIS Building, University of Tsukuba	From domestic institutions: 126 From overseas institutions: 56
Sep 28-30, 2014	Aging Sciences: Tsukuba Global Science Week Held at University of Tsukuba	From domestic institutions: 649 From overseas institutions: 15
Sep 25, 2014	Title: The 68th Fujihara Seminar Venue: IBM Amagi Homestead	From domestic institutions: 39 From overseas institutions: 24
Sep 24, 2014	Title: “Homeodynamics in Clock, Sleep and Metabolism” (The 3rd Annual IIIS Symposium) Venue: The University of Tokyo	From domestic institutions: 215 From overseas institutions: 17
Jan 20, 2014	Title: The 2nd Annual IIIS Symposium Venue: International Congress Center, Tsukuba	From domestic institutions: 121 From overseas institutions: 22
Mar 27, 2013	Title: The 1st Annual IIIS Symposium Venue: International Congress Center, Tsukuba	From domestic institutions: 169 From overseas institutions: 30

Appendix 5 List of Achievements of Center's Outreach Activities between FY 2012 – 2018

* Using the table below, show the achievements of the Center's outreach activities from FY2012 through FY2018 (number of activities, times held).

*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 below, 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.

Activities	FY2012 (number of activities, times held)	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018
PR brochure, pamphlet	1	2	2	2	1	1	2
Lectures, seminars for the general public	0	8	5	12	20	24	24
Teaching, experiments, training for elementary, secondary and high school students	0	4	9	10	12	15	17
Science cafe	1	2	2	0	1	2	4
Open house	1	0	10	1	0	1	5
Participating, exhibiting in events	0	4	6	3	3	3	3
Press releases	1	4	3	6	8	25	17
Publications of the popular science books	2	0	0	1	0	3	2

Appendix 5 List of Media Coverage of Projects Carried out between FY 2012 – 2018

* Select main items of press releases, media coverage, and reports for FY 2012-2018 (especially by overseas media)

1) Japan

No.	Date	Type of the media (e.g., newspaper, magazine, television)	Description
1	Oct 31, 2012	**Newspaper** The Asahi Shimbun, The Yomiuri Shimbun, The Mainichi, The Nikkei, Ibaraki Shimbun, Nikkei Business Daily	Establishment of International Institute for Integrative Sleep Medicine, University of Tsukuba
2	Apr 26 - May 24, May 4 -25, 2013	**Newspaper** Chugoku Shimbun Kobe Shimbun	Introduction of Yanagisawa's research history and current research works (weekly) (Yanagisawa)
3	May 14, 2013	**Newspaper** Fukui Shimbun	Solving the mystery of sleep (Yanagisawa)
4	Jun 18, 2013 Jun 20, 2013	**Newspaper** The Yomiuri Shimbun, The Mainichi, The Nikkei,Ibaraki Shimbun, Tokyo Shimbun, Nikkei Sangyo Shimbun The Asahi Shimbun	Scientists revealed that the quality of prior waking experience greatly influence sleepiness (Yanagisawa)
5	Aug 9, 2013	**Magazine** Beikoku Seiyaku Gyokai Shuho (U.S. Pharmaceutical Industry Weekly Report) Vol. 481	Masashi Yanagisawa's vision – challenges in medicinal chemistry to develop orexin agonist from academia in Japan (Yanagisawa)
6	Sep 1, 2013	**Magazine** Medical Asahi Vol. 502	Challenging the mystery of sleep / wakefulness (Yanagisawa)
7	Sep 17 - 18, 2013	**Newspaper** Nikkei Sangyo Shimbun	Innovators in Japan (1)(2) Scientists discovered that a neuropeptide is involved in the mystery of sleep (Yanagisawa)
8	Sep 25, 2013	**Newspaper** The Nikkei	Discovery of gene adjusting length of sleep (Yanagisawa)

9	Sep 30, 2013	**Magazine** AERA Mook	Introduction of Yanagisawa's research history and current achievements (Yanagisawa)
10	Nov 29, 2013	**Magazine** Nikkei Science Janary 2014	"The Front Runner" Solving the mystery of sleep by genetics and neuroscience (Yanagisawa)
11	Dec 6, 2013 Dec 12, 2013	**Newspaper** The Nikkei, Nikkei Sangyo Shimbun Mainichi Shimbun	Discovery of unknown hormone secretion control mechanism responsible for anxiety in the adrenal cortex (Yanagisawa)
12	Jan 14, 2014	**Newspaper** Mainichi Shimbun	Revealing the mechanisms of the sleep disorder narcolepsy (Sakurai)
13	Jan 24, 2014	**Television** Science Zero, NHK	Development of novel drugs based on protein crystallization technique under a low-gravity environment in the International Space Station (Urade)
14	Jan 31, 2014	**Television** Koichi Dohmoto's a little bit of science, NHK	Discovery of "Sleep Gene"? (Yanagisawa)
15	Feb 2, 2014	**Television** Koji Kato's interview "Koji's Soul," BS4	Discovery of orexin involved in appetite and sleep (Sakurai)
16	Mar 2, 2014	**Television** Yume no tobira plus, TBS	Why do we sleep? Challenges to solve the mystery of sleep (Yanagisawa)
17	May 5, 2014	**Magazine** President, Issue 2014 5.5	Will new drugs controlling sleep/wake regulation be developed? (Yanagisawa)
18	May 25, 2014	**Television** Galileo X, BS Fuji	Mystery of sleep/wakefulness: exploring sleepiness from genetic point of view (Yanagisawa)
19	Jun 10, 2014	**Newspaper** The Nikkei	Scientists elucidate the molecular mechanisms underlying itch and scratching behavior (Nagase)
20	Aug 10, 2014	**Magazine** Nikkei Business Associe Issue 2014.9	How to sleep well for business persons (Yanagisawa)
21	Sep 1, 2014	**Magazine** Ushio September Issue	Interview by Soichiro Tahara: innovator of Japan (Yanagisawa)
22	Sep 20, 2014	**Newspaper** The Yomiuri Shimbun	Top scientist describes the mystery of sleep: Yomiuri Techno Forum (Yanagisawa)
23	Sep 25, 2014 Sep 26, 2014	**Newspaper** Yomiuri Shimbun Nikkan Kogyo Shimbun	Eight scientists were awarded Teiichi Yamazaki Award: Foundation for Promotion of Material Science and Technology of Japan (Nagase)

24	Nov 13, 2014	**Telvision** World Business Satellite, TV Tokyo	Feature: new drug saves sleepless people in Japan (Yanagisawa)
25	Nov 15, 2014	**Radio** Prime Factor, J-WAVE	World-leading scientist explains the importance of sleep (Yanagisawa)
26	Nov 23, 2014	**Television** Galileo X, BS Fuji	Development of active chemical compounds that can penetrate into blood brain barrier (Yanagisawa, Nagase)
27	Dec 3, 2014	**Magazine** The Nikkei Biotech Online	Interview of Teiichi Yamazaki Award laureate (Nagase)
28	Dec 3, 2014	**Magazine** Medical Tribune MTPro	Nalfurafine may improve the quality of sleep (Nagase)
29	Dec 4, 2014	**Newspaper** The Yomiuri Shimbun	Development of the new drug that may cure insomnia by directly acting on sleep center in brain (Yanagisawa)
30	Dec 13, 2014	**Magazine** Igaku No Ayumi vol. 251 No. 11	Synthesis of nalfurafine hydrochloride that may become a remedy for generalized pruritus (Nagase)
31	Feb 24, 2015	**Magazine** GQ Japan	Your Internal Clock (Yanagisawa)
32	Mar 2, 2015	**Book** Yume No Tobira Plus	Rescuing people suffering from sleep disorders (Yanagisawa)
33	Mar 5, 2015	**Television** NHK News	Scientists identified cells responsible for regulating circadian rhythms (Yanagisawa)
34	Mar 13, 2015	**Newspaper** The Mainichi	Warning to 'sleepless country'; Yanagisawa emphasizes the importance of sleep (Yanagisawa)
35	Mar 19, 2015	**Newspaper** The Asahi Shimbun	Scientists identified cells responsible for regulating circadian rhythms (Yanagisawa)
36	May 2015	**Magazine** Medical Asahi, May 2015 issue	Series: Drugs born in Japan volume 10 "Bozentan" (Yanagisawa)
37	Jun 2015	**Magazine** Medical Asahi, June 2015 issue	Series: Drugs born in Japan volume 11 "Suvorexant" (Yanagisawa)
38	Aug 10, 2015	**Radio** Radio Nikkei 1, "Byoyaku Hour"	Regulation of sleep/wakefulness; orexin system as a drug target (radio lecture by Yanagisawa)
39	Aug 13, 2015	**Newspaper** The Mainichi	Towards the mystery of sleep: challenges of IIIS (Yanagisawa)

40	Sep 29 - Oct 1, 2015	**Newspaper** The Daily Engineering & Consruction News, The Yomiuri Shimbun **Web** Medical Tribune Aging Style	International Institute for Integrative Sleep Medicine, University of Tsukuba: Construction of IIIS Building completed and the inauguration ceremony was held
41	Oct 1, 2015	**Newspaper** The Mainichi	Q & A: How to maintain good quality of sleep in the refuge (Yanagisawa answered an interview by newspaper)
42	Oct 11, 2015	**Television** NHK	Science ZERO "Mystery of Sleep: The frontier of sleep medicine" (Yanagisawa)
43	Oct 22 – 27, 2015	**Newspaper / Web** The Asahi Shimbun, The Yomiuri Shimbun, The Mainichi, The Nikkei Biglobe News, MyNavi News *And other 22 coverages	New insights into the role and function of REM sleep (Hayashi)
44	Oct 23, 2015	**Television** NHK News	New insights into the role and function of REM sleep (Hayashi, interview by telephone)
45	Dec 3, 2015	**Newspaper** The Asahi Shimbun	Discovery of a novel compound regulating wakefulness (Nagase)
46	Dec 27, 2015	**Television** TBS	Yume-no-tobira plus "Dream compounds making us sleep well" (Urade)
47	Jan 8, 2016	**Magazine** Bungei Shunju Feb issue	Feature article: Qualification for the leaders making breakthroughs (Yanagisawa interview)
48	Jan 25 - Feb 4, 2016	**Newspaper** The Asahi Shimbun, The Joyo Shimbun **Web** Aging Style	Timing is important for the care of PTSD (Sakaguchi)
49	Feb 4, 2016	**Newspaper** The Yomiuri Shimbun	Feature article: orexin and sleep (Yanagisawa)
50	Feb 26, 2016	**Television** BS Fuji	Kakushin-no-ism (Yanagisawa)
51	Mar 14, 2016	**Newspaper** Nikkei Sangyo Shimbun	Innovative studies on substances regulating sleep (Yanagisawa)

52	Apr 16, 2016	**Television** NHK E-tele	"Why do animals sleep -Sleep Science-" (Sakurai)
53	Apr 28, 2016	**Television** NHK NEWS **Newspaper** The Ibaraki Shimbun, The Asahi Shimbun, The Mainichi, The Yomiuri Shimbun, The Sankei Shimbun, Tokyo Shimbun	Yanagisawa received the Medal with Purple Ribbon (Yanagisawa)
54	Jun 16, 2016 Sep 1, 2016	**Television** NHK E-tele **Newspaper** The Nikkan Kogyo Shimbun	A new device to stop snoring (Satoh)
55	Aug 10, 2016	**Newspaper** Nikkei Shimbun	Introduction of highly internationalized institute, IIIS (Yanagisawa, Vogt, etc.)
56	Sep 6 - 8, 2016	**Newspaper** The Yomiuri Shimbun, The Nikkan Kogyo Shimbun, Nikkei Sangyo Shimbun, The Asahi Shimbun	Hayashi received the 26th Tsukuba Encouragement Prize (Hayashi)
57	Sep 8, 2016	**Magazine** Tarzan	Sleep associated with body and brain condition (Sakurai)
58	Oct 20, 2016	**Radio** Radio NIKKEI	Mechanisms of sleep/wake regulation and the discovery of a novel neurotransmitter (Yanagisawa)
59	Oct 23, 2016	**Television** BS JAPAN	Mirai Eyes (Introduction of research activities in IIIS)
60	Nov 3, 2016 - Jan 13, 2017	**Television / Newspaper / Web** ANN NEWS, NHK News, Kyodo News, The Asahi Shimbun, GIZMODO *And other 48 coverages	Genetic analysis identifies proteins controlling sleep in mice (Yanagisawa, Funato)
61	Nov, 2016	**Magazine** Rikejo	"What is good sleep?" (Hayashi)
62	Dec 26, 2016	**Magazine** Magazine	Mechnisms in the brain controlling appetite (Sakurai)
63	Jan 10, 2017	**Magazine** Tsukuba Style	Healthy lunch boxes of scientists (Vogt etc.)

64	Jan 16 - Feb 2, 2017	**TelevisionWeb** NHK News **Newspaper/Web** The Asahi Shimbun	Direct link between REM sleep loss and the desire for sugary and fatty foods (Lazarus)
65	Feb 16, 2017 Feb 23, 2017	**Web** The Asahi Shimbun Degital, YOMIURI ONLINE	Orexin as a potential drug for treating septic shock (Yanagisawa, Hayashi)
66	Feb 23, 2017	**Television** NHK Sogo TV	TV coverage of a IIIS faculty member
67	Mar 1 - 22, 2017	**Newspaper/Web** The Nikkan Kogyo Shimbun, The Nikkey Sangyo Shimbun, YOMIURI ONLINE	Gene therapy for the Schizophrenia model mice (Hayashi)
68	Apr 7, 2017	**Magazine** CREA Bungeishunju	Interview (Sakurai)
69	Apr 11, 2017 Sep 15, 2017 Oct 19, 2017	**Web** Mynavi News, AERA dot. **Magazine** junior AERA	Does loss of sleep cause obesity? (Lazarus)
70	Apr 14 - Apr 27, July 26, 2017	**Web** Hazard Lab, NEWS SALT, University Journal Online, The Mainichi Shimbun, academist Journal **Newspaper** The Ibaraki Shimbun	Memory can be manipulated using auditory stimuli during sleep (Sakaguchi)
71	Apr 19, 2017	**Television** NHK WORLD TV	Sleep Science (Yanagisawa)

72	May 16 - Jun 19, 2017	**Newspaper** The Nihon Keizai Shimbun, The Ibaraki Shimbun, The Mainichi Shimbun, The Nihon Keizai Shimbun, The Asahi Shimbun, The Nikkan Kogyo Shimbun **Web** Medial News QLifePro **Radio** CBC RADIO	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy (Yanagisawa)
73	July 2, 2017	**Web** Medial News QLifePro	The secret connection between anxiety and sleep (Sakurai)
74	Sep 27, 2017 Oct 3, 2017	**Web** Mynavi News **Newspaper** Zaikei Shimbun	Cannabis, “Spice” – better think twice (Urade)
75	Oct 2, 2017	**Television** Asaichi	Interview: "Possible to gain beauty and health?" (Sakurai)
76	Oct 19 - Dec 18, 2017	**Web** University Journal Online, academist Journal, Nature Asia **Newspaper** The Nikkan Kogyo Shimbun	Why do we fall asleep when bored? (Lazarus)
77	Nov 22, 2017	**Web** anannews	Interview: "No worries if you are a night preson! A professional advices you suibable ways for sleep" (Sakurai)
78	Nov 23, 2017	**Magazine** Tarzan	Interview: "7 keys to improve your sleep" (Sakurai)
79	Nov 23, 2017	**Web** anannews	Interview: "Can we talk to a sleep-talker? Sleep Q&A" (Sakurai)
80	Nov 24, 2017 Nov 30, 2017	**Web** Medial News QLifePro, University Journal Online	A neuropeptide that regulates behavior: a key to ease excessive fear (Sakurai)
81	Nov 25, 2017	**Web** GIZMODO JAPAN	Interview: A mastermind of sleep/awake? Secret power of Orexin which controls sleep (Yanagisawa)
82	Nov 25, 2017	**Web** ananweb	Interview: "Prime time" is a lie!? New common sense of sleep you should know (Sakurai)

83	Nov 28, 2017	**Magazine** anan	Interview: "Have a best sleep with the very latest science"(Sakurai)
84	Dec 2, 2017	**Web** Nikkei Health	Interview: Recommendation of mouth tape for better sleep (Satoh)
85	Dec 3, 2017 Mar 11, 2018	**Television** Mainichi Broadcasting System	Interview: Behavoir while sleeping (Sakurai)
86	Jan 1 - 22, 2018	**Web** JIJI PRESS, Sankei News **Newspaper** The Asahi Shimbun	The Asahi Prize 2017 (Yanagisawa)
87	Mar 3 - May 18, 2018	**Newspaper** The Yomiuri Shimbun, The Asahi Shimbun, The Mainichi Shimbun **Web** Healthy Living, SEKAI SUIMIN KAIGI, JB press	Crowdfunding project of sleep study on human (Yanagisawa, Satoh, etc.)
88	Apr 3, 2018 Jun 28, 2018	**Newspaper** The Mainichi Shimbun **Web** My Carat	Sleep disorder risk factors among student athletes (Tokuyama, Sato, etc.)
89	May 2, 2018	**Web** NIKKEI BP	Interview about Orexin (Sakurai)
90	May 7 - Jun 13, 2018	**Newspaper** The Asahi Shimbun, The Yomiuri Shimbun ONLINE	An unexpected chemosensor pathway for innate fear behavior against predator odor (Liu, Yanagisawa, etc.)
91	Jun 13 - Nov 27, 2018	**Newspaper / Web / Magazine** Nikkei Shimbun, Kyodo News, The Asahi Shimbun, SEKAI SUIMIN KAIGI, Newton, NIKKEI SCIENCE, WIRED *And other 50 coverages	Reversible Changes to Neural Proteins May Explain Sleep Need (Liu, Yanagisawa, Funato)
92	Jun 26, 2018	**Web** My Carat	The secret connection between anxiety and sleep (Sakurai)
93	July 7, 2018	**Magazine** Newton	Interview: Solving the mystery of sleep (Yanagisawa)

94	July 20, 2018 July 26, 2018	**Newspaper** THE SCIENCE NEWS **Web** Medical Tribune	How the mammalian brain sexually differentiates – hypothalamic Ptf1a confers the competence (Fujiyama)
95	Aug, 2018	**Magazine** National Geographic	Want to Fall Asleep? Read This Story. (Sakurai, Human Sleep Lab, etc.)
96	Sep 6, 2018 Sep 12, 2018	**Television / Web** Abema News	Interview about IIIS and human sleep lab (Yanagisawa, Morita, etc.)
97	Sep 14 - 15, 2018	**Newspaper** The Yomiuri Shimbun, The Mainichi Shimbun, The Nikkan Kogyo Shimbun, Ibarakinews, Nikkei Shimbun	The Keio Medical Science Prize (Yanagisawa)
98	Oct 10, 2018	**Web** Tarzan web	Why do people get sleepy? What is a sleeping debt? Approaching the mystery of sleep from three keywords (Sakurai)
99	Oct 22, 2018	**Newspaper / Web** Nikkei Shimbun	Interview about Mobile Sleep Laboratory (Yanagisawa, F-MIRAI)
100	Nov 19, 2018	**Newspaper / Web** Nikkei Shimbun, Nikkei Biotechnology & Business	S'UIMIN Received ¥700 Million in Capital from Mirai Creation Fund (S'UIMIN, Yanagisawa)
101	Nov 30, 2018 Feb 28, 2019	**Web** TEIJIN	Interview (Yanagisawa)
102	Dec 5, 2018	**Magazine** Newton	Interview about his sleep research and SNIPPs (Yanagisawa)
103	Jan 6, 2019	**Newspaper** Nikkei Shimbun	Interview "My story" (Yanagisawa)
104	Feb 8, 2019	**Television** NHK "Tohoku-kokokara"	Interview about Human Calorimeter (Tokuyama, Ishihara)
105	Mar 26, 2019	**Web** Kodansha BLUE BACKS WEB	Interview about link between sleep and PTSD treatment (Sakaguchi, Soya)
106	Mar 26, 2019	**Magazine** Newton	Interview about adrenaline (Sakurai)

107	Mar 30, 2019	**Newspaper** Weekly Toyo Keizai	Interview: Why do people sleep? Driving the world in sleep research (Yanagisawa)

2) Overseas

No.	Date	Type of the media (e.g., newspaper, magazine, television)	Description
1	May 16, 2014	**Web** YouTube channel: Science 200 Miles in the Sky (Boeing)	ISS Discovery: Fighting Duchenne's Muscular Dystrophy (Urade)
2	July 1, 2015	**Web** NASA Official Website	ISS Benefits For Humanity: Hope Crystallizes (Urade)
3	Sep 8, 2015	**Television** NHK World	“Medical Frontiers” Volume 5, Sleep (Yanagisawa)
4	Oct 26, 2015	**Web** nippon. com	Solving the Riddle of Slumber: Cutting-Edge Research Hub in Tsukuba Focuses on Sleep (Yanagisawa) *Translaed in 8 languages
5	Nov 2 - 8, 2016	**Television / Newspaper / Web** NBCDFW.com, Science Daily, ResearchGate *And other 15 coverages	Genetic analysis identifies proteins controlling sleep in mice (Yanagisawa, Funato)
6	May 17, 2017	**Web** Asian Scientist Magazine	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy (Yanagisawa)
7	May 30, 2017	**Web** Medical Xpress	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy (Yanagisawa)
8	May 30, 2017	**Web** CLUSTER SALUD	Hope: Solid first steps to develop a cure for narcolepsy (Yanagisawa) *in Spanish
9	July 1, 2017	**Web** Science Daily	The secret connection between anxiety and sleep (Sakurai)
10	July 6, 2017	**Web** Asian Scientist Magazine	The secret connection between anxiety and sleep (Sakurai)

11	July 7, 2017	**Web** Sleep Review	The secret connection between anxiety and sleep (Sakurai)
12	Sep 5, 2017	**Web** Science Daily	Cannot sleep due to stress? Here is the cure (Urade)
13	Sep 5, 2017	**Web** Sleep Review	Sugarcane Active Component Restores Stress-affected Sleep (Urade)
14	Sep 10, 2017	**Web** Medical News Today	Sugarcane extract may relieve stress-induced insomnia (Urade)
15	Sep 21, 2017	**Web** Science Daily	Cannabis, 'spice' – better think twice (Urade)
16	Sep 29, 2017	**Web** Science Daily	Why do we fall asleep when bored? (Lazarus)
17	Sep 30, 2017	**Web** Financial Express	Why do we fall asleep when bored? (Lazarus)
18	Oct 4, 2017	**Web** Seeker	Why do we fall asleep when bored? (Lazarus)
19	Oct 24, 2017	**Web** ReliaWire	Why We Still Don't Understand Sleep, And Why It Matters (Yanagisawa)
20	Dec 11, 2017	**Web** Genetic Literacy Project	Chasing a cure for narcolepsy—and why it should be a priority (Yanagisawa)
21	Jan 1, 2018	**Web** The Atlantic	Why do we need to sleep? (Yanagisawa)
22	Mar 20, 2018	**Web** Intellectuals	Sleep Needs and Sleep Mystery (Yanagisawa) in Chinese
23	May 21, 2018	**Web** EurekAlert!, Alpha Galieo	An unexpected chemosensor pathway for innate fear behavior against predator odor (Liu, Yanagisawa, etc.)
24	Jun 1, 2018	**Web** Courrier International	Sciences.Why are we sleeping? (Yanagisawa) *in French

25	Jun 13 - Aug 25, 2018	**Web** EurekAlert!, NNR, Technology Networks, Science Daily, ZME Science, DALLAS NEWS, Sleep Review, Forbes, Quanta Magazine, WIRED US, infosalus.com	Reversible Changes to Neural Proteins May Explain Sleep Need (Liu, Yanagisawa, Funato)
26	Aug, 2018	**Magazine** National Geographic	Want to Fall Asleep? Read This Story. (Sakurai, Human Sleep Lab, etc.)
27	Sep 24 - 26, 2018	**Web** EurekAlert!, Science Daily, Biosicence Technology, Laboratory Equipment, BAZAAR	Never Enough Sleep? Mouse Mutation Shown to Increase Daily Amounts and Need for Sleep (Honda, Yanagisawa)
28	Dec 23, 2018	**Web** Noti-America	The journalist with narcolepsy that can teach you to sleep better (Yanagisawa) *in Spanish
29	Mar 15, 2019	**Web** Rossiya Segodnya	World Sleep Day (Yanagisawa) *in Russian
30	Mar 23, 2019	**Magazine** nature INDEX 2019 JAPAN	Interview (Yanagisawa, Cherasse)

Appendix6-1 Host Institution's Commitment (Fund, Personnel)

1. Contributions from host institution

(1) Fund, Personnel

* Regarding "Fund" entry, describe with reference to the items in the Progress Report (Jisseki-hokoku-sho) based on Article 12 of the Grant Guidelines (Kofu-yoko).

* Don't include competitive funding obtained by researchers (used as research project funding)

(FY 2012-2018)

<Fund> **(million yen)**

Fiscal Year	2012	2013	2014	2015	2016	2017	2018
Personnel	22	22	22	36	36	36	36
Faculty members	0	0	0	14	14	14	14
Full-time	0	0	0	0	0	0	0
Concurrent	0	0	0	14	14	14	14
Postdocs	0	0	0	0	0	0	0
RA etc.	0	0	0	0	0	0	0
Research support staffs	0	0	0	0	0	0	0
Administrative staffs	22	22	22	22	22	22	22
Full-time	16	16	16	16	16	16	16
Concurrent	6	6	6	6	6	6	6
Project activities	10	10	10	10	10	10	10
Travel	0	0	0	0	0	0	0
Equipment	0	0	0	0	0	0	0
Research projects	0	0	0	0	0	0	0
Total	32	32	32	46	46	46	46

<Personnel> **(person)**

Fiscal Year	2012	2013	2014	2015	2016	2017	2018
Personnel	3	3	3	4	4	4	4
Faculty members	0	0	0	1	1	1	1
Full-time	0	0	0	0	0	0	0
Concurrent	0	0	0	1	1	1	1
Postdocs	0	0	0	0	0	0	0
RA etc.	0	0	0	0	0	0	0
Research support staffs	0	0	0	0	0	0	0
Administrative staffs	3	3	3	3	3	3	3
Full-time	2	2	2	2	2	2	2
Concurrent	1	1	1	1	1	1	1

Appendix6-1 Host Institution's Commitment

1. Contributions from host institution

University of Tsukuba has provided IIIS with various resources as support. The provided support is equal to or greater than the support planned in the application for the WPI program.

(2) Provision of land and/or building(s), lab space, etc.

Resources provided by University of Tsukuba as support for IIIS

1) University of Tsukuba established the Organization for the Support and Development of Strategic Initiatives, and IIIS received 10 million JPY in management expenses grants as support from the initiative every year.
2) Support was launched for research funding and also with applications for competitive funding.
3) Support the part of the personnel cost of Vice Center Director, Sakurai.
4) Measures were taken to provide personnel costs for 3 administrative positions for university personnel engaging in the key areas of general affairs and accounting. From July, 2015, arranged one URA to the research strategy and management team.
5) From FY2015 University support more than 80 million yen as the expenses for utility of the IIIS building from the indirect cost though university collected 70 million yen as the rental fee for own funding area of 2,000 m^2.
6) Support was provided for the research spaces of the Health and Medical Science Innovation Laboratory, University of Tsukuba Hospital E Building, Project Research Building and TARA Center, providing 5,000 square meters divided among the listed venues until the completion of relocation to the new research building in August 2015.
7) From April 2019, University supports the research spaces at Innovation Medical Research Institute to expand IIIS activity especially for the human physiology laboratory.

2. System under which the center's director is able to make substantive personnel and budget allocation decisions

Division of authority

All key matters concerning the operation in the institute have been decided by a top-down system of the Director as shown in 5-1.

Principal Investigators' meeting (PI meeting)

According to the establishment of IIIS, led by the administrative department, a PI meeting was established, during which the PI regularly submits opinions to the Center Director to determine important matters concerning the IIIS as shown in 5-1.

IIIS personnel committee

IIIS established a personnel committee to improve the way of researcher's appointment as shown in 5-1.

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

From FY2015 at University of Tsukuba, a quantitative evaluation index concerning research performance in terms of published papers and writings, granted external funding, and research alliance with public and for-profit organizations, is being established. We also establish an evaluation system with merit-based compensation considering the same index at University shown in 5-3.

Tenure of PI

In the third mid-term plan of University of Tsukuba, a strategic framework of research resources including tenure positions over the entire university will be set out and it will be planned to reallocate them based on evaluation of research activities/achievements of Faculties and research centers in the third mid-term plan of University of Tsukuba. According to results of the evaluation, University of Tsukuba promise 13 tenure positions could be allocated to IIIS by the end of FY2022 as following; Director and vice director have already been appointed as tenure position. In FY 2019, three faculties (Dr. Arisa Hirano the female PI, Dr. Yu Hayashi PI and Dr. Noriki Kutsumura PI candidate) are appointed to the tenure. From FY2020 to FY2023, eight PIs, two PIs at every year, are appointed to the tenure.

3. Support for the center director in coordinating with other departments at host institution when recruiting researchers, while giving reasonable regard to the educational and research activities of those departments

Teaching qualification

12 with Comprehensive Human Science Biomedical Sciences major (doctoral programs), 11 with Comprehensive Human Science Medical Sciences major (master's programs), 6 with Comprehensive Human Science Kansei, Behavioral and Brain Sciences major (doctoral programs), 10 with Ph. D. Program in Human Biology (HBP), 2 with Ph.D. Program in Life Science Innovation（T-LSI), one with Pure and Applied Sciences Chemistry major, and 12 with Ph. D. Program in Humanics have a teaching qualification as shown in 6-4.

4. Revamping host institution's internal systems to allow introducing of new management methods

(e.g., English-language environment, merit-based pay, cross appointment, top-down decision making unfettered by conventional modes of operation)

Constitution of the administrative department

Administrative department is operated by the following four teams (General affairs, Accounting, Research strategy & management and Alliance & Communication) led by the Administrative Director as shown in 5-2.

Use of English as official language and employment of bilingual staff

English is used as an official language at IIIS. A bilingual environment has been implemented, with 70% of administrative staff members fluent in spoken and written English as shown in 5-2.

Joint appointment system

With the purpose of enabling the Center Director to occupy concurrent posts at University of Tsukuba and UTSW, the joint appointment system was newly introduced to University of Tsukuba in March 2014. The University made the joint appointment of Dr. Yanagisawa as of April 1, 2014, Dr. Liu from FY2014 with UTSW. We also made domestic joint appointment for Dr. Morita from April 1, 2018 with Forest Research and Management Organization (FRMO) in Tsukuba. In addition, we made three way joint appointment for Dr. Liu among NIBS, UTSW and Tsukuba as shown in 5-3.

A dispensation of distributing license revenues to research centers/departments

University of Tsukuba agree that, after deduction of the compensation for inventors and 10% of overhead expenses, licensing revenues received by the University should be distributed to the headquarters and IIIS in proportion to IP cost burdens (refer 5-3 for details).

5. Utilities and other infrastructure support provided by host institution

(*In addition to those listed in the item 1. "Contributions from host institution")

Cost of constructing a new research building

The Sleep Medicine Research Building costed approximately 3.8 billion yen and the expenses beyond those covered by the facility development subsidies of 2 billion yen kindly provided by MEXT were supported by in-house funding as shown in as shown in 5-4.

6. Support for other types of assistance

Expansion of activities of the professor specially appointed

The president of University of Tsukuba decided to appoint one of PIs in IIIS, Dr. H. Nagase became 70 years old in FY2017 and essential for the success IIIS to "Tokumei-kyoju," the professor specially appointed by the President.

Appendix6-2 The Host Institution's Mid-term Plan

* Excerpt the places in the host institution's "Mid-term objectives" and/or "Mid-term plan" that clearly show the positioning of the WPI center within its organization.

An excerpt from "University of Tsukuba Third Mid-term Goals and Mid-term Plans" as of April 2018

4. Goals and plans for promoting research of the world's highest level

In broad academic disciplines, we will develop leading-edge research at the world's highest level in both research that deeply explores the truth and research aimed at returning research results to society.

Mid-term Goal 10

We will steadily proceed with fundamental research by reviewing and consolidating our existing research center system, and we will work toward making a major leap forward in interdisciplinary research through the introduction of new systems and cooperation with universities and other institutions in Japan and other countries.

◇*Specific measures for the steady implementation of fundamental research and making a major leap forward in interdisciplinary research*

Mid-term Plan 25

We will form international joint use and joint research centers in fields where our university has strengths and notable characteristics such as mathematical and material science, environmental energy, information computational science, life and medical sciences, humanities and social sciences, and sports science by strengthening cooperation with research institutes including universities in Japan and overseas, engaging in interactive joint research and large-scale international joint research, and inviting overseas research units to the university.

Mid-term Plan 26

We will further accelerate our priority research support by promoting research at the world's highest level centered on research at the WPI International Institute for Integrative Sleep Medicine, the Center for Computational Sciences, the Life Science Center of Tsukuba Advanced Research Alliance (TARA), the Institute for Comparative Research in Human and Social Sciences, Tsukuba-Plant Innovation Research Center, and Shimoda Marine Research Center.

KPI: Achieve the world's top 100 ranking in a considerable number of research areas

Mid-term Goal 12

We will undertake bold reforms in research systems within the university.

◇*Specific measures for bold reforms in research systems within the university*

Mid-term Plan 29

We will promote fundamental research, interdisciplinary research and research based on the university's strategy in a sound manner. Furthermore, to make support and the granting of authority to research organizations consistent throughout the organizations and based on an assessment, we will classify the research organizations roughly into the advanced research centers and the research and development centers. For the advanced research centers, we will conduct their assessments every five years, taking into account results of reviews for the reorganization, restructuring, and consolidation of research centers, and will introduce a system of certification (four levels: R1-R4). The research and development centers will cover all of their management and activity costs through external funds, and will engage in research activities aimed at social implementation.

Furthermore, along with the introduction of this system, we will convert research centers into education and research support centers, consolidate and restructure the research centers, and reorganize the research centers into research units, based on results of research center reviews we have conducted to date.

R1: World-level research center R2: National-level research center

R3: Priority development research center R4: Training research unit

KPI: By 2016, formulate a plan for reorganizing, restructuring and consolidating all research centers, and hereafter proceed with the reorganization, restructuring and consolidation in succession according to the plan.
Organize and implement rules by 2018 so that the content and standard of support for each research center and the authority granted to each research center within the university correspond to the level of the center, and are consistent throughout the university.

Mid-term Plan 29-2

As well as strategical promotion of research activity focusing on the "Faculty" (as shown below), at the time of introducing the mechanism for assessing the advanced research centers as listed in Plan 29, we will grant authority to manage personnel affairs fitting the specific needs to the research organizations as shown below, which has been certified as R1 world- level research center, to enable flexible and swift employment of faculty members based on the strategical promotion of research activity in the priority areas.

Faculty

Faculty of Humanities and Social Sciences, Faculty of Business Sciences, Faculty of Pure and Applied Sciences, Faculty of Engineering, Information and Systems, Faculty of Life and Environmental Sciences, Faculty of Human Sciences, Faculty of Health and Sport Sciences, Faculty of Art and Design, Faculty of Medicine, Faculty

of Library, Information and Media Science, Faculty of Transdisciplinary Research

R1 world-level research center

Center for Computational Sciences, the Life Science Center of Tsukuba Advanced Research Alliance (TARA)