

Summary of Proposal (Compile in English within 3 pages.)

Host institution: University of Tsukuba
Head of host institution: Kyosuke Nagata, President
Research center: International Institute for Integrative Sleep Medicine
Center director: Masashi Yanagisawa
Chief center-project officer (in December 2012): Masashi Yanagisawa
Administrative director: Toshio Kokubo

1) Project summary

Sleep is a remarkably universal phenomenon in the higher animal species, and its disturbances reduce mental and physical wellbeing. However, the function of sleep and the mechanism for sleep regulation still remain unknown; these questions are among the most important challenges in modern neuroscience. The Research Center has gathered the world prominent scientists from multiple research fields contributing to the neurobiology of sleep. We aim at elucidating the fundamental mechanism of sleep/wake regulation by combining the cutting-edge methodologies of basic biology covering molecular genetics, cell biology and neuroscience. We are inducing the fusion of the basic biology, pharmaceutical sciences and experimental medicine in order to reveal the pathophysiology of sleep disorders and related diseases, and to develop methods for their treatment and prevention. Through these research efforts, we are striving to reduce sleep disorders and associated diseases, and to contribute to an improvement of physical and mental health in today's aging society with a dwindling birthrate.

2) Mission statement and/or center's identity

The mission of this WPI Center is to be a multidisciplinary, international hub for the research to elucidate the fundamental mechanism of sleep/wakefulness, to develop strategies to regulate sleep, and to contribute to enhancement of world health through the combat with sleep disorders and associated diseases.

3) Research fields

Name of the target research field Sleep science

Sleep science, as defined here, is an inherently interdisciplinary field in terms of methodology, being comprised of 3 research fields, basic biology, pharmaceutical sciences and experimental medicine. Each research field is also a multidisciplinary field, i.e., basic biology spans molecular genetics, cellular biology, neurophysiology, and neurochemistry, while pharmaceutical sciences cover medicinal chemistry, pharmacology and drug discovery. Experimental medicine includes clinical physiology, psychiatric medicine, clinical molecular genetics and social medicine. While focusing on sleep, the target research field is also interdisciplinary with respect to its integral research targets, e.g., studying mood disorders as well as metabolic diseases that are closely associated with pathological variations in sleep/wake states.

Importance of the target research field

Sleep is a behavior that everyone experiences daily and it takes up as much as one third of one's entire lifetime. 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 increase the risk of mood disorders such as depression. The society demands the development of strategies to remedy sleep disorders and associated diseases.

Research trend of this field

As for the current trend of the field, triggered by the reports by Yanagisawa that a deficiency of the hypothalamic neuropeptide OREXIN is the root cause of the then-mysterious sleep disorder NARCOLEPSY, a consensus has been formed by most researchers in the field that orexin constitutes one of the centerpieces of the neural circuitry regulating sleep and wakefulness. Moreover, one of global pharmaceutical companies, MSD launched a new class of sleeping pills targeting the orexin pathway recently and many drug companies follow it, indicating the consensus among the pharmaceutical industries that this field is highly important for drug discovery.

Reasons why the project fit for this call for proposals

Japan has been producing a number of researchers who have made significant accomplishments in the field of sleep science. Masashi Yanagisawa and Takeshi Sakurai discovered the neuropeptide orexin and unraveled pathophysiological mechanisms of narcolepsy. This is arguably one of the most significant discoveries in the past 50 years of sleep research, which has created a new avenue of inquiry in the field: the two papers describing the discovery of orexin and the narcolepsy phenotype in orexin knockout mice have been cited more than 4,400 times combined. While primarily focusing on sleep, they have been conducting various behavioral studies that are related to sleep. Hiromasa Funato and Yanagisawa elucidated the potent role of orexin in basal metabolism and body weight regulation, uncovering the possibility of drug discovery for metabolic diseases. In part due to the wide recognition of these contributions, Yanagisawa was selected as one of the Principal Investigators for the FIRST Program of the Cabinet Office of Japan, which allowed him to intensively promote sleep research at his new Center hosted by the University of Tsukuba.

4) Research objectives

The research objectives that the Center seeks to achieve are: 1) elucidation of the fundamental mechanisms of sleep/wake, 2) elucidation of molecular pathogenesis of sleep disorders and related diseases, and 3) development of treatments for sleep disorders.

5) Outline of management

Establish a top-down administrative system headed by the Center Director by fully utilizing his long-term experience at an American university.

Under the supervision of the Administrative Director who is thoroughly knowledgeable in the research contents of the center and has rich experiences in establishing new research institutes at the pharmaceutical companies, the administrative staff are composed of the Administrative Director, Vice Administrative Director, and the following 4 teams. (General coordination and planning team, Financial accounting team, Research strategy and management team, Alliance and communication team).

Decision-making system

In order to facilitate efficient and flexible administration of the research center, the Center Director has the sole authority of decision-making related to the personnel and management matters within the Center, except for the removal of himself and the determination of his own salary. Regardless of the position, anyone who is participating in this Center can offer his/her opinions regarding the management or treatment directly to the Center Director.

Allocation of authority between the center director and host institution

The President of the University has the authority to elect or dismiss the Center Director. The Center Director has a wide range of authorities regarding the general management and internal administration of the research center.

6) Researchers and other center staffs, satellites, partner institutions

Principal Investigators: 24 (foreigners 6) (Achieved by March 2022), Total Researchers: 62 (foreigners 21) (Achieved by March, 2022), Total Staff at Core-Center: 101 (Achieved by March, 2022), Main principal investigators: Masashi Yanagisawa, Hiromasa Funato, Takeshi Sakurai, Yoshihiro Urade, Robert Greene, Qinghua Liu, Hiroshi Nagase, Makoto Sato, Ichiyo Matsuzaki, Hitoshi Shimano, Kumpei Tokuyama, Akiyoshi Fukamizu, Satoru Takahashi, Tetsuo Shimizu, Carla Green, Joseph Takahashi, Yang Dan, Hitoshi Okamura, John Renger, Satellite: University of Texas Southwestern Medical Center, Akita University, University of California, Berkeley, Kyoto University, Merck Sharp and Dohme.

7) Outline of research environment

(1) Establish a strong supportive organization in order to decrease the burden of administrative obligations of scientists so that they concentrate on their research. (2) Reduce the burden of administrative obligations of researchers and allow them to devote themselves exclusively to their research. (3) Take advantage of Tsukuba as a research city in providing living support for foreign researchers. (4) Provide a sufficient amount of startup research funding and strong administrative support when applying for external funding through the entire application process for the independent researchers. (5) Conduct international recruitment to hire post-doctoral fellows. (6) English is used as the official language at the research center. (7) Adopt a system for evaluating achievements and merit-based compensation. (8) Provide appropriate equipment and facilities, office and animal center (8,000m²) as a top world-premier research center. (9) Hold international symposia once a year, and invited seminar series twice a month.

8) Outline of indicators for evaluating a center's global standing

i) Criteria and methods to be used for evaluating the center's global standing in the subject field

1. Number of citations of published papers in the medium to long term. 2. Positions and scientific accomplishments of the alumni (trainee) of the research center. 3. Funding

ii) Results of current assessment made using said criteria and methods

1. The number of citations for the article that reported the discovery of orexins is 4,264 and for the article describing narcolepsy episodes in orexin-deficient mice, the number of citations are 2,515. 2. Many researchers who received trainings as post-doctoral fellows in Yanagisawa Lab have become professors and assistant professors of domestic and overseas universities, working in responsible positions in research institutions and corporate settings. 3. The total amount of competitive external funding available for the IIIS Core Team in FY2016 reached 6.10 million US\$.

iii) Goals to be achieved through the project (at time of final evaluations)

1. The citation indices of our publications surpass those at other premier research centers for sleep science, such as the Stanford Center for Sleep Sciences and Medicine. 2. More senior alumni of the research center have attained independent positions in the academia and in the industry, both domestic and overseas. 3. Maintain the level of research grant acquisition at FY2016.

9) Securing research funding

The University of Tsukuba is responsible for the labor costs for the vice center director, 5 Collaborative PIs who were full-time faculties at the University before participating in this research center, and for the 3 full-time University staffs who are appointed to the administrative division of this research center. The University supported ¥1.8 billion for the costs of new research building, facilities, equipment, landscaping and for moving into the new building. Further, light, heating and water utility costs of the building are spent by the University as a major financial support for the operation of the Center.

10) Appropriations plan

Appropriations plan	FY	2017	2018	2019	2020	2021	Total
(Exchange Rate: JPY/USD=100)	Cost (\$ millions)	5.85	5.85	5.85	5.85	5.85	29.25

(Exchange Rate: JPY/USD=100)

11) Summary of host institution's commitment

How positioned within the host institution's mid-to-long-term strategy plan

The Midterm Goals states: "strive for deep specialized expertise, open up new cross-disciplinary fields, and achieve research results which are outstanding by international standards," and "ambitiously open up new cross-disciplinary fields." The WPI is in complete agreement with the University's Midterm Goals and Midterm Plan. We specified "International Institute for Integrative Sleep Medicine" for a Midterm Plan in FY2012.

Concrete Measures

- 1) Provide at least the same level of resources as funded by this project.
- 2) Enable top-down decisions by the Center Director regarding personnel affairs and budgets.
- 3) Make necessary adjustments to assemble persons from other institutes/faculties of the University.
- 4) Amend the regulations to accommodate the new system of management.
- 5) Provide 8,000m² of floor space that a "globally visible" premier research center deserves.
- 6) Support to sustain the Center after this program ends.

Research Center Project (in English)

Host institution: University of Tsukuba

Head of host institution: Kyosuke Nagata, President

Research center: International Institute for Integrative Sleep Medicine

Center director: Masashi Yanagisawa

Chief center-project officer (in December 2012): (Masashi Yanagisawa, Center for Behavioral Molecular Genetics, Professor and Director (in December 2012))

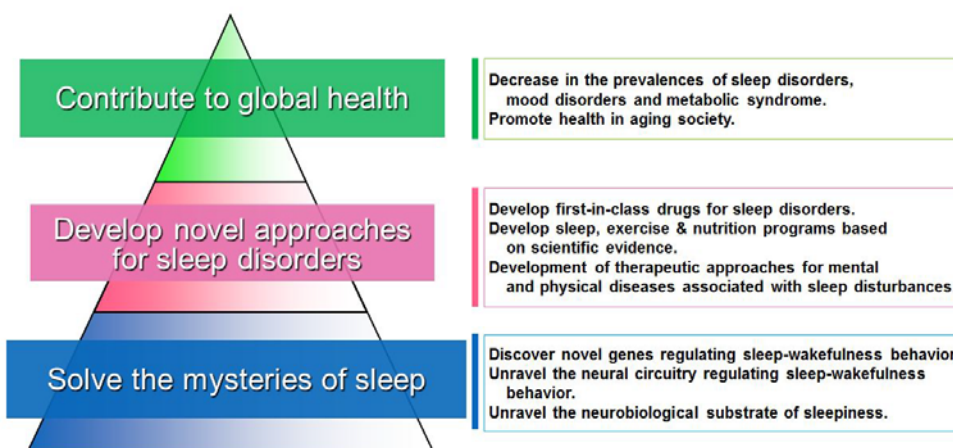
Project summary

- Briefly describe the general plan of the project.

Sleep is a remarkably universal phenomenon in the higher animal species, and its disturbances reduce mental and physical wellbeing. However, the function of sleep and the mechanism for sleep regulation still remain unknown; these questions are among the most important challenges in modern neuroscience. The research center established as International Institute for Integrative Sleep Medicine (IIIS) has gathered the world prominent scientists from multiple research fields contributing to the neurobiology of sleep. They cooperate together to elucidate the fundamental principles of sleep/wake regulation, and develop new strategies to assess and treat sleep diseases as well as the closely associated metabolic and mental disorders.

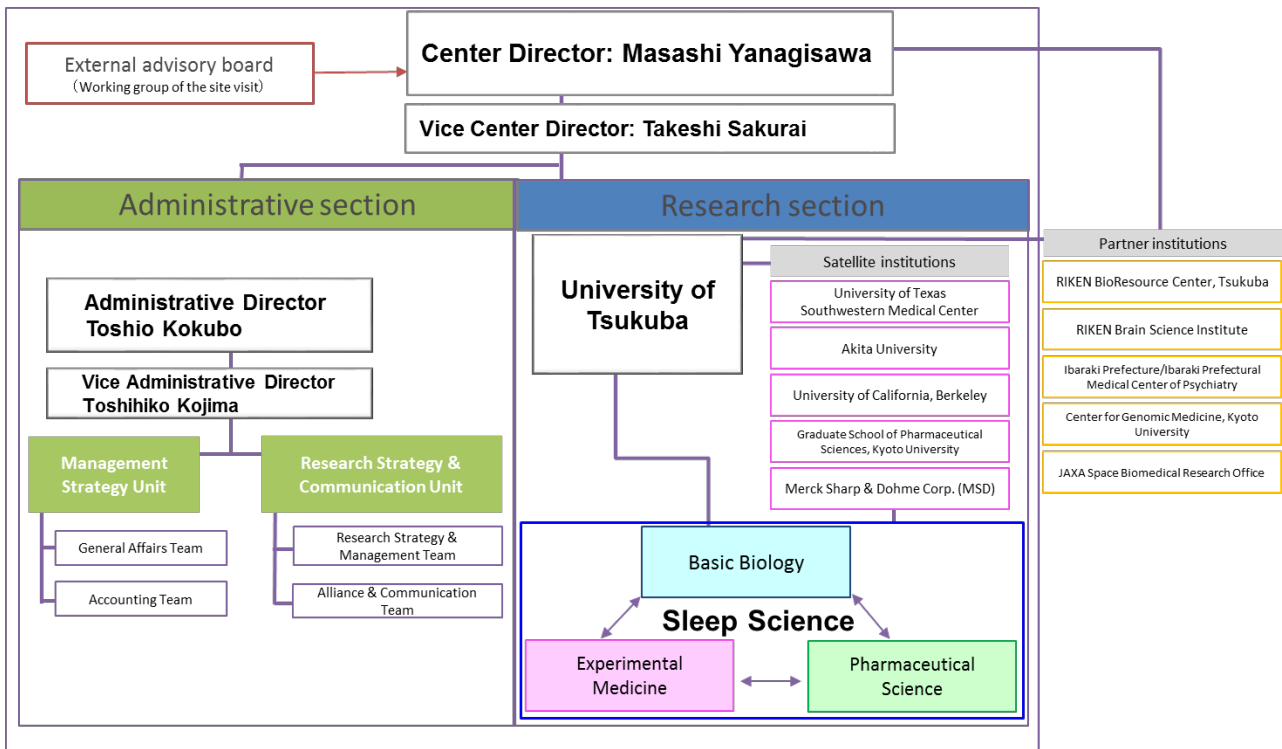
The general plan of the project

At the Center, we aim at elucidating the fundamental mechanism of sleep/wake regulation by combining the cutting-edge methodologies of basic biology covering molecular genetics, cell biology and neuroscience. We are inducing the fusion of the basic biology, pharmaceutical sciences and experimental medicine in order to reveal the pathophysiology of sleep disorders and related diseases, and to develop methods for their treatment and prevention. Through these research efforts, we are striving to reduce sleep disorders and associated diseases, and to contribute to an improvement of physical and mental health in today's aging society with a dwindling birthrate.



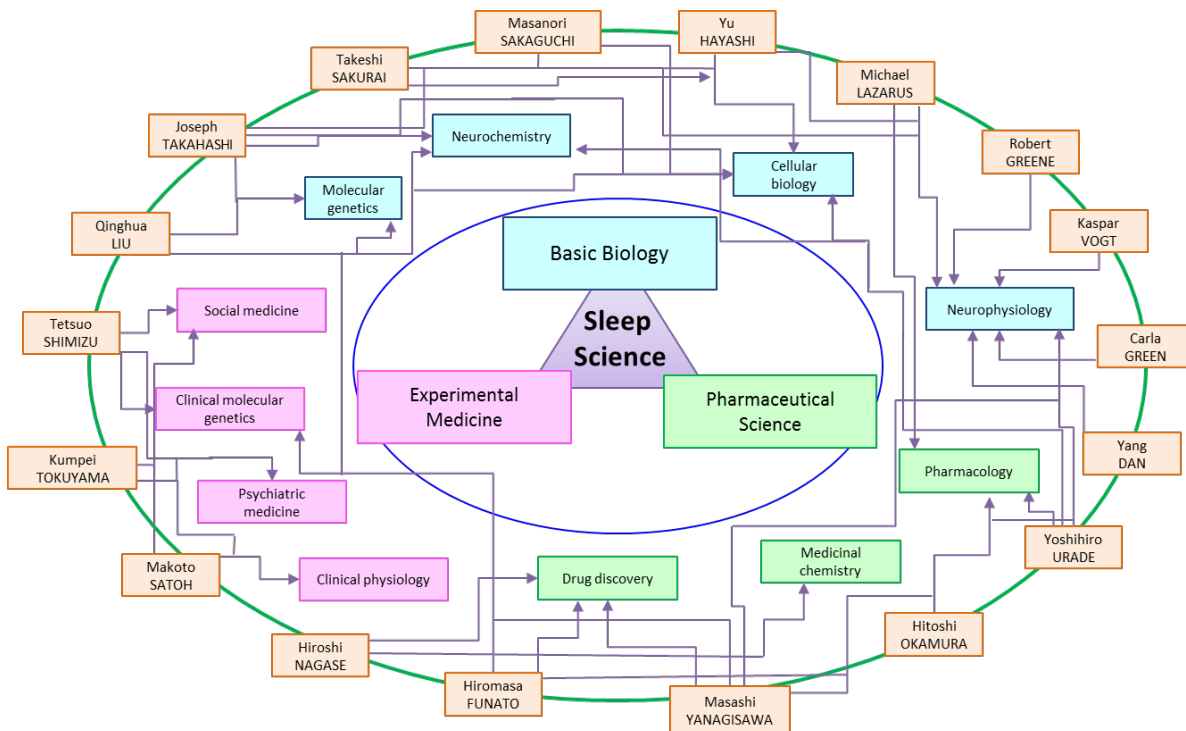
The Center's overall structure

The administrative structure provides the Center Director with sufficient authority to enable a timely and flexible decision-making. The University of Tsukuba hosts the Core site, while the Satellites are located at the University of Texas Southwestern Medical Center, University of California, Berkeley, Merck Sharp and Dohme (MSD), Kyoto University and the Akita University. Although several research "groups" are depicted, the Center constantly encourages the exchange of information, materials and personnel among and beyond these groups in order to facilitate the creation of new ideas and the fusion of research fields.



The Center's multidisciplinary network of Principal Investigators and research targets/objectives

Towards the Center's unified research goals, world-class Principal Investigators (PIs) who are working in related but distinct research fields and employing different methodologies, closely cooperate with each other while having their specific research targets and objectives.



<Major changes from initial project plan:>

There are no major changes from the initial project plan, which have been implemented just with minor modifications, e.g., appointment of young prominent scientists to Jr. PIs such as K. Vogt, M. Sakaguchi, M. Lazarus, and Y. Hayashi, according to the Center Director's policy to create a new style of research center by learning from merits and virtues in the organization of "department" in major US universities. PIs running their lab independently are to be appointed regardless of their age and career stage in the Center. According to advices/recommendations by the working group of the site visit, we strive to implement translational research with which achievements of basic biology and pharmaceutical sciences should be translated to experimental medicine, and additional PIs, M. Sato and K. Tokuyama, were appointed to expand the clinical group in the Center.

<Mission statement and/or center's identity>

- Briefly and clearly describe the mission statement and/or the project's identity as WPI center.

The mission of this WPI Center is to be a multidisciplinary, international hub for the research to elucidate the fundamental mechanism of sleep/wakefulness, to develop strategies to regulate sleep, and to contribute to enhancement of world health through the combat with sleep disorders and associated diseases.

1. Research fields

- Specifying the inter-disciplinary field(s) to which the project may be closely related.
- Describe the importance of the proposed research, including domestic and international R&D trends in the field and Japan's advantages.
- If centers in similar fields already exist in Japan or overseas, please list them.

Name of the target research field

Sleep science

Sleep science, as defined here, is an inherently interdisciplinary field in terms of methodology, being comprised of 3 research fields, basic biology, pharmaceutical sciences and experimental medicine. Each research field is also a multidisciplinary field, i.e., basic biology spans molecular genetics, cellular biology, neurophysiology, and neurochemistry, while pharmaceutical sciences cover medicinal chemistry, pharmacology and drug discovery. Experimental medicine includes clinical physiology, psychiatric medicine, clinical molecular genetics and social medicine. While focusing on sleep, the target research field is also interdisciplinary with respect to its integral research targets, e.g., studying mood disorders as well as metabolic diseases that are closely associated with pathological variations in sleep/wake states and sleep deficiencies.

Importance of the target research field

Sleep is a behavior that everyone experiences daily and it takes up as much as one third of one's entire lifetime. From ancient times, natural philosophers and scientists have been fascinated by sleep, especially by its association with loss of consciousness and dreaming. 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 increase the risk of mood disorders such as depression. In developed countries, the prevalence rate of sleep disorders that prevent people having healthy sleep is around 15%, with the lifetime prevalence more than 30%. The underlying factors behind this problem include the increasingly nocturnal lifestyle of today's societies, presence of shift workers who account for about 20% of the working population, and an increase of the elderly population. Deficiencies in healthy sleep cause significant social losses, and are linked to car accidents due to excessive sleepiness, increased prevalence of mood disorders, increased suicide deaths, and an increased caregiving burden due to wandering and delirium in the elderly. Thus, while sleep has been a perpetual topic of scientific inquiry that keeps attracting many great minds, it is also a field where the

society demands the development of strategies to remedy sleep disorders and associated diseases. On this account, the importance of sleep as the target research field is clear.

As for the current trend of the field, triggered by the reports by Yanagisawa, Mignot, Siegel and their colleagues that a deficiency of the hypothalamic neuropeptide OREXIN is the root cause of the then-mysterious sleep disorder NARCOLEPSY, a consensus has been formed by most researchers in the field that orexin constitutes one of the centerpieces of the neural circuitry regulating sleep and wakefulness. Moreover, one of global pharmaceutical companies, MSD launched a new class of sleeping pills targeting the orexin pathway recently and many drug companies follow it, indicating the consensus among the pharmaceutical industries that this field is highly important for drug discovery.

Existing domestic and overseas research centers in similar fields

The University of Tsukuba Center for Behavioral Molecular Genetics, which was the foundation of this WPI Center, had been the only multi-investigator research center in Japan that is specifically focusing on sleep science. This was operated under the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program) of the Cabinet Office of Japan, entitled "Molecular Mechanism and Control of Complex Behaviors," with Masashi Yanagisawa as the Core Investigator. As for sleep research centers in overseas countries, a number of large research institutes around the world host such sites: More than 10 centers in the U.S., including the Stanford Center for Sleep Sciences and Medicine; two research centers in England; and some additional in other countries such as Australia. Most of them, however, focus on clinical aspects of sleep and sleep disorders.

Reasons why the project fit for this call for proposals

1) Japan's expertise and international appeal

Japan has been producing a number of researchers who have made significant accomplishments in the field of sleep science. In particular, contributions to narcolepsy research have been immense, including Yutaka Honda who was the first to elucidate an important association between narcolepsy and immunity. Masashi Yanagisawa and Takeshi Sakurai discovered the neuropeptide orexin and unraveled pathophysiological mechanisms of narcolepsy. This is arguably one of the most significant discoveries in the past 50 years of sleep research, which has created a new avenue of inquiry in the field: the two papers describing the discovery of orexin and the narcolepsy phenotype in orexin knockout mice have been cited more than 6,800 times combined. While primarily focusing on sleep, they have been conducting various behavioral studies that are related to sleep. Hiromasa Funato and Yanagisawa elucidated the potent role of orexin in basal metabolism and body weight regulation, uncovering the possibility of drug discovery for metabolic diseases. In part due to the wide recognition of these contributions, Yanagisawa was selected as one of the Principal Investigators for the FIRST Program (2009-2013) of the Cabinet Office of Japan, which allowed him to intensively promote sleep research at his new Center hosted by the University of Tsukuba.

Japanese researchers have also contributed prominently to the studies on sleep-inducing substances. Especially noteworthy are the discovery of the sleep-inducing effect of prostaglandin D2 by Osamu Hayaishi and Yoshihiro Urade, and the revelation of its molecular mechanisms through the adenosine pathway. As seen here, the accumulation of sleep researchers' continuous efforts and accomplishments, as well as the research environment that made it possible, constitute Japan's strong expertise in the field of sleep science. Moreover, the present WPI-Focus allowed Yanagisawa to fully base his research back in Japan as the full-time Center Director, moving from the University of Texas Southwestern Medical Center (UTSW) where he conducted his research for over 20 years. His presence is further elevating the level of Japan's expertise in sleep science.

The international appeal of creating a center in Japan for the target research field owes in part to numerous contributions made by Japanese researchers in this field and related research areas. The Center has an international appeal to it not only because of the Japanese researchers gathered there but also the participation of the several prominent US researchers best represented by Joseph Takahashi, who has made Nobel-worthy contributions to uncover the molecular mechanisms underlying circadian rhythms including the discovery of one of the first clock genes. The pool of these prominent researchers makes the Center further internationally appealing, which attracts younger talents around the world.

However, while being attracted to the excellent research accomplishment and environment of Japan, it is true that there are many among foreign researchers who feel uneasy about living and conducting research in Japan. Here, having Yanagisawa as the leader is a great help. Yanagisawa had been based at an American university for over 20 years while sustaining his mental identity as Japanese; his experiences (both as an US-based researcher returning back to Japan, and as a person who lived in US as a “foreign immigrant”) allows him to manage the Center by creating a research environment that is friendly to foreign researchers. Building on top of the strong tradition of Japan’s sleep research, the Center aims to become an international hub of sleep science by gathering excellent young researchers from within and outside of Japan.

2) Future development and sustained, multidisciplinary research accomplishments

Despite the recent progress, it is fair to say that the field of sleep science is still in a very naive and immature state compared to other fields of behavioral neuroscience. There have only been relatively limited strings of definitive findings such as the importance of orexin. The circadian rhythm research saw an explosive progress after Takahashi’s discovery of the *Clock* gene. In this analogy, today’s sleep neurobiology looks as if it is the night before the impending discovery of its own “Clock.” However, this also means that a similarly explosive progress in sleep science will likely start in the near future. We will aim at seizing that moment. Moreover, sleep/wakefulness is closely tied with energy metabolism, and the associations between sleep disorders and metabolic syndrome are expected to become an increasingly major topic in sleep science in the near future. This center, pursuing the interface of sleep/rhythm and metabolism as one of its main research objectives, is well prepared for the future.

At the University of Tsukuba Center for Behavioral Molecular Genetics led by Yanagisawa, that was the basis of the development to the Center, we fully operated a large-scale sleep recording system for mice (capable of simultaneously EEG sleep-record from up to 100 mice), as well as a cutting-edge, real-time optical visualization system for the neuronal activity in deep brain structures. As for the generation and cross-breeding of genetically engineered mouse strains that can frequently become the rate-determining step for the research, we produced numerous mouse lines for cell type-specific and time-dependent control of multiple genes of interest, including the orexin related genes. Thus, we had already established a core of the cutting-edge research environment; the implementation of the Center allowed us to expand and improve this core environment into a globally visible, long-term sustainable hub of multi-investigator cooperation.

In order to make Center into a truly interdisciplinary site for the “fusion of research fields,” the following researchers have participated: Hiroshi Nagase, who has an outstanding track record in the field of medicinal chemistry, including his successes in developing first-in-class, marketed drugs in two different clinical areas; Akiyoshi Fukamizu, who has been making outstanding contributions to the understanding of the molecular mechanisms of metabolic syndrome and hypertension through intracellular signaling pathways and the regulation of gene transcription; and Hitoshi Shimano, who has made significant accomplishments in lipid metabolism and lipid-induced intracellular signaling pathways. The active participation of these researchers facilitates the integration of research themes interfacing sleep/wake regulation, cellular metabolism, and the endocrine control, aiming at the creation of a new research modality.

We realize that the flow and provision of new ideas from the clinical setting back to the research laboratory is essential for the long-term sustained development of top-notch research, e.g., suggesting a hypothesis based on findings gained from sleep disorder patients that can be tested in a mouse model. Participating in the Center for this purpose is Tetsuo Shimizu, one of the very few psychiatry professors in Japan who is specialized in sleep disorders. Since many of the researchers who participate in the Center use genetically engineered mice as their routine resources, Satoru Takahashi also actively participates, who was the Director of the Laboratory Animal Resource Center at the University of Tsukuba. His core-facility support has been essential, including the generation, transportation and management of transgenic mice.

Thus, the Center, while having its sharp focus on sleep science, has a truly multidisciplinary pool of researchers gathered from within and outside Japan. Having top researchers with varying backgrounds and methodologies closely interacting together under a unified research focus allows the Center to sustain

a world-class level of research in the target field for long term.

2. Research objectives

- Describe in a clear and easy-to-understand manner the research objectives that the project seeks to achieve by the end of the grant period. In describing the objectives, the following should be articulated in an easily understandable manner: What kind of research do you plan to implement by fusing various fields within the environmental domain? In the process, what world-level scientific issues are sought to be resolved? What is the expected impact of the scientific advances to be achieved on society in the future?
- Describe concretely the research plan to achieve these objectives.

The research objectives that the Center seeks to achieve are: 1) elucidation of the fundamental mechanisms of sleep/wake, 2) elucidation of molecular pathogenesis of sleep disorders and related diseases, and 3) development of treatments for sleep disorders.

1) Elucidation of the fundamental mechanisms of sleep/wake

[Research objectives to be accomplished by the end of the grant period]

- **Identification of new key genes involved in sleep/wake regulation.**
- **Understanding the mechanistic principles of neural circuitry for sleep/wake regulation.**

Our current knowledge on sleep/wake regulation is actually quite limited when judged under the rigorous standards of today's neuroscience. Among the limited tidbits is the notion that the lateral hypothalamic orexin neurons and the wake-active monoaminergic and cholinergic neurons of the classical ascending activation system, together with the sleep-active GABAergic neurons of the preoptic hypothalamus, likely constitute important parts of the executive circuitry for sleep/wake switching. Orexin neurons are clearly important for the stability of the switch. We know that the sleep-inducing substance adenosine (which is blocked by caffeine) is importantly involved in the regulation of the "depths" of non-REM sleep. We know that these executive systems are powerfully governed by the circadian clock in the suprachiasmatic nucleus and by the presumed "sleep homeostat" somewhere in the brain. Overall, our current level of understanding is rudimentary at best. We thus conduct precise neurophysiological analyses of these known components. We also dissect neuronal and molecular mechanisms of sleep regulation by circadian clocks and sleep-inducing substances. At the same time, we use a completely blind (unbiased) genetic approach in order to identify new and unexpected genes that are importantly involved in the regulation of sleep/wake.

[Approaches necessary to accomplish research objectives]

a. Forward genetic approach to identify new key genes involved in sleep/wake regulation (Yanagisawa, Funato, Takahashi J and Liu)

Considering the current state of the field where the fundamental principles of sleep/wake regulation are still hidden inside a black box, an unbiased approach that strategically triggers serendipity is essential in order to get closer to the very nature of sleep. Under the situation, we believe that the best approach is the forward genetics in mice that Takahashi used beautifully when discovering the *Clock* gene without having a biological hypothesis. The forward genetic screen of randomly mutagenized mice for abnormal sleep/wake patterns was initially started as a collaboration of Yanagisawa and Takahashi, J at UTSW. The project had then been expanded as one of the major pillars of the FIRST Project at the University of Tsukuba, where we also collaborated with Shigeharu Wakana at RIKEN BioResource Center in Tsukuba. The large-scale screening at Tsukuba was carried out smoothly with a sustained throughput of 60-80 mice screened per week. We had screened ~8,000 mice by EEG/EMG-based true sleep analysis by the end of the FIRST Project, and detected more than 10 pedigrees of mice exhibiting marked, heritable abnormalities in sleep/wake. The forward genetics project was handed over to the Center at the stage of identifying the causative gene by SNP-based linkage mapping and whole-exome sequencing, while continuing the primary screen in a limited scale. The heritable sleep abnormalities so far confirmed include: substantially increased non-REM sleep time (*Sleepy*), and markedly abnormal REM sleep architecture (*Dreamless*). These strong phenotypes have been confirmed to be caused by mutations in the genes of *Sik3* and *Nalcn*, respectively. We will directly close in on the regulatory molecular mechanisms of sleep/wake by analyzing their functions and studying signal transductions/pathways involving them.

b. Optogenetic and pharmacogenetic approach to understand the mechanistic principles of neural circuitry for sleep/wake regulation (Yanagisawa, Sakurai, Sakaguchi, Lazarus, Hayashi and Liu)

Orexin is clearly required for normal sleep/wake control; orexin deficiency causes narcolepsy, in which a highly destabilized sleep/wake states is the salient feature. However, we still do not fully understand how exactly orexin functions to promote wakefulness and stabilize sleep/wake switching. We are pursuing various novel optogenetic and pharmacogenetic technologies in order to real-time visualize as well as manipulate the activities of specific neuronal populations involved in sleep/wake control. Yanagisawa and Sakurai, long-term collaborators, have been establishing sophisticated experimentation systems using the latest, cutting-edge technologies available in today's neuroscience. Liu is an expert on the RNAi pathway, which he has been dissecting through sophisticated biochemistry. At the Center, he has jumped in to the field of sleep neurobiology and collaborated with Yanagisawa to examine functions of the genes identified by the forward genetics by biochemical approaches including proteomics. By combining these various methods, we are clarifying the principles of neural circuit operation that controls sleep/wake behaviors.

c. Elucidation of the mechanisms of action of sleep substances (Urade, Lazarus, Vogt and Greene)

Urade and Lazarus have investigated the mechanism for the sleep-inducing action of prostaglandin D2 and discovered that it is mediated by adenosine. Greene has generated and examined brain-specific adenosine receptor-deficient mice, and found out that the effect of sleep deprivation on the depths of non-REM sleep is remarkably reduced under a deficient adenosine signaling. However, because adenosine is ubiquitously present and can be generated and metabolized by all cell types, it has been difficult to elucidate how its local extracellular concentration is regulated in a manner that is relevant for sleep regulation. At this research center, the mechanisms of action of sleep-inducing substances, especially that of adenosine, are further investigated and how it relates to the homeostatic mechanism of the sleep/wake is examined.

d. Elucidation of the function of REM sleep (Hayashi)

The function of REM sleep is one of the largest mysteries in neuroscience. During REM sleep, both cortical neural activity and blood flow increase. To address the roles of REM sleep, we succeeded in identifying neurons in the brainstem that either inhibit REM sleep or promote REM sleep, and establishing transgenic mice in which REM sleep can be artificially suppressed or increased. As a result, we found that artificial suppression or induction of REM sleep attenuates or enhances slow wave activity (SWA) during subsequent NREM sleep, respectively. The results implicate REM sleep promotes SWA, which is important for memory consolidation and synaptic plasticity. To further elucidate the beneficial roles of REM sleep, effects of increasing or reducing REM sleep are studied with various neurological disease models.

2) Elucidation of molecular pathogenesis of sleep disorders and related diseases

[Research objectives to be accomplished by the end of the grant period]

- **Identification of a molecular link between intracellular events and sleep-related behaviors *in vivo*.**

Irregular sleep/wake cycle and insomnia are a risk factor for metabolic syndrome as well as for mood disorders. However, the mechanism for the link is unknown. Using genetically engineered mouse models, the possible molecular links between sleep/wake, mood regulation, and metabolic control are studied.

[Approaches necessary to accomplish research objectives]

a. Establishment of a REM sleep behavior disorder (RBD) model and translational research using the orexin antagonist (Yanagisawa, Funato)

Increasing attention has been paid to REM sleep behavior disorder (RBD) as a prodromal marker of Parkinson's disease and related neurodegenerative diseases. To develop a good animal model of RBD is crucial for understanding the pathophysiology of RBD and developing therapeutic intervention for it. Based on our hypothesis that disrupted glycinergic system underlies RBD symptoms, we have systematically examined *Gla1*-gene modified mice using Cre-loxP system. We then succeeded in

developing RBD model mice ($Glra1^{flox/flox};ChAT-Cre^{Cre/wt}$) which displayed gross body and limb movements including running, jerking and chewing during REM sleep. Our RBD model is anticipated to serve as a good platform of screening for a novel drug for treating RBD.

b. Forward genetics to understand the molecular basis of fear and fear/anxiety disorders (Liu)

Emotions define the essence of being human and are powerful drivers of behaviors. Fear is a basic emotion that enhances animal survival by triggering the fight, flight or freeze responses to perceived danger. Almost nothing is understood about fear at the molecular level. We have been conducting a forward genetic (from phenotype to gene) screen, based on a novel predator odor-induced innate fear assay that we developed, to identify mutations that either mitigate or accentuate innate fear in mice. Our studies may usher in a new era of molecular investigations into the fundamental principles of fear, and open doors for the treatment of many fear/anxiety disorders, including post-traumatic stress disorder (PTSD), general anxiety disorder, general or specific phobia, and obsessive compulsive disorder (OCD).

3) Development of new treatment methods for sleep disorders

[Research objectives to be accomplished by the end of the grant period]

- **Develop drug-candidate compounds for sleep-related disorders which advance to clinical trial**
- **Develop the “good sleep” program, a multidimensional non-drug intervention, to prevent sleep-related disorders based on the evidence of basic and clinical studies.**

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

[Approaches necessary to accomplish research objectives]

a. Development of drug-candidate compounds targeting orexin receptors (Nagase, Yanagisawa, Funato)

Triggered by the discovery of the prominent role of orexin in maintenance of wakefulness by us and others, several pharmaceutical companies have developed orexin receptor antagonists. The most advanced of those antagonists, suvorexant from Merck, was launched as the first-in-class sleep-inducing drug in Japan and US in 2014. We are taking a novel and opposite approach: instead of inducing sleep at bedtime, our drug shall elevate the level of wakefulness during daytime and that will naturally bring about sound sleep at night. Orexin receptor agonists should be also useful as the mechanistic replacement therapy for orexin-deficient individuals, accounting for >90% of narcolepsy patients. Agonists may also prevent and reduce metabolic syndrome, since Funato has demonstrated that orexin is a net-negative regulator of energy homeostasis. Towards these goals, we carried out a high-throughput screening of a library of ~250,000 drug-like compounds at UTSW and identified hits of several distinct chemical classes of orexin receptor agonists. Based on information obtained by this screening, we have embarked upon a serious medicinal chemistry efforts in order to further improve compounds' potency, blood-brain-barrier permeability, and oral bioavailability. We fully realized that making a CNS-available agonist for peptidergic receptor was a formidable challenge in medicinal chemistry, but Nagase's experience of creating two first-in-class marketed drugs made it possible to create a promising lead, YNT-185 showing a reasonable *in vivo* efficacy.

b. Identification of novel sleep/wake modulating substances and their mechanism of action by *in vivo* screen of compound libraries (Urade)

We have focused on the development of sleep promoting substances from foods or traditional medicines. We first screened hundreds of natural products (extract or major ingredient) by monitoring locomotor activity with passive infrared sensor. Compounds showed significant decreasing (or increasing) locomotor activities were measured sleep by monitoring electroencephalogram (EEG)

and electromyogram (EMG) combined with locomotor activities. We analyzed the EEG and EMG data by the automated analytical system "Sleep sign" developed by collaboration with company. We identified sleep promoting 8 compounds and 1 extract, among which 2 products have been launched as food supplements by Fujifilm Corporation and Lion Corporation. We continue the collaboration to elucidate their mechanisms.

3. Management

i) Center director

- Provide the name of the center director, his/her age (as of 1 April 2017), specialties, and brief career profile (within 5 lines).
- If there is a plan to change the center director, how does the new center director intend to construct the center and what is his/her vision of objectives to be achieved? Provide a synopsis written by the new center director (free format).

Masashi Yanagisawa (Age: 56), M.D., Ph.D. Specialties: Neuroscience, Pharmacology. Associate Professor of Molecular Genetics, University of Texas Southwestern Medical Center at Dallas (UTSW); Associate Investigator, Howard Hughes Medical Institute (1991), Professor, UTSW; Investigator, HHMI (1996-2014); Director, Yanagisawa Orphan Receptor Project (JST/ERATO) (2001-2007); a member of National Academy of Sciences (2003-Present); Professor and Director, FIRST program, U of Tsukuba (2010-2014); Director, IIS, U of Tsukuba (2012-Present).

ii) Administrative director

- Provide the name of the administrative director, his/her age (as of 1 April 2017), and his/her brief career profile (within 5 lines).

Toshio Kokubo (Age: 61), Ph. D. Specialties: Protein engineering, Cellular engineering, Drug Discovery. Ph. D., Kyoto University (1983); Postdoctoral fellow, Rockefeller University (1983-1987); Ciba-Geigy Japan Ltd. (1987-1997); Bayer Ltd. (1997-2002); Senior Director of Biomedical Research Laboratories, Takeda Pharmaceutical Co. Ltd. (2002-2013); Vice-Administrative director, IIS, University of Tsukuba (2013), Administrative director, IIS, U of Tsukuba (2013-Present).

iii) Composition of administrative staff

- Concretely describe how the administrative staff is organized.

We have established a strong supportive organization in order to decrease the burden of administrative obligations of scientists so that they concentrate on their research, and to enable prompt decision-making and resolute implementation. The strong administration increases the independence and autonomy of the Center and establishes a top-down administrative system headed by the Center Director. Moreover, by fully utilizing the long-term experience of the Center Director at an American university, we have put persistent efforts to reassess the research and administrative organizations. In addition, by assigning a few full-time members of the University administrative staff to the Center, we are making best use of the University's know-how and also enable an organic coordination with the administrative organization of the University.

1. Composition of the administrative staff

Under the supervision of the administrative director who is thoroughly knowledgeable in the research contents of the center and has rich experiences in establishing new research institutes at the pharmaceutical companies, the administrative staff are composed of the administrative director, vice administrative director, and the following four teams.

- General Coordination and Planning Team (3 staff members)
General Coordination and Planning Team is engaged in legal affairs, general affairs, personnel affairs, employment, travel, work management, and management for safety and hygiene. Two full-time University staff members who have a thorough knowledge of general affairs are assigned to the Center.
- Financial Accounting Team (3 staff members)
Financial Accounting Team is responsible for budget management and execution, procurement, and domestic and overseas transfer of funds and supplies. One full-time University staff member who has a thorough knowledge of budgetary and accounting is assigned to the Center.
- Research Strategy and Management Team (3 staff members)

Research Strategy and Management Team is in charge of a wide variety of tasks related to research strategy, project management, competitive research funds, including information collection, application support, support for report preparations, overseas alliance and research alliance. One full-time University Research Administrator (URA) who is highly experienced in the affairs for securing research funds and knowledgeable of the governmental systems is assigned to the Center.

- Alliance and Communication Team (3 staff members)

Alliance and Communication Team conducts public relations (outreach activities), annual IIIS symposia, PI meeting, IIIS seminar series, lectures open to the public, and other WPI joint events. With regard to the support for a large number of foreign researchers coming to the Center, we take full advantage of the City of Tsukuba as an international scientific research park, and commission it to the Japan International Science and Technology Exchange Center (JISTEC) as required.

We recruit Ph. D. scientists that have experiences of drug discovery and /or liaison officer in industries for three key positions in the administration, i.e., Administrative Director, the leader of Research Strategy and Management, and the leader of Alliance and Communication, to act as an interface between researchers (the Center Director and PIs) and the administrative staffs without scientific background in the administration as well as the university headquarters.

2. Use of English as the official language

English is used as an official language at the research center. All assigned staff members are fluent in spoken and written English, except for the people who have specific skills that cannot be replaced by any other people. Documentation is in English or bilingual as much as possible, except where it has to be in Japanese for external reasons.

3. Recruitment and development of quality staff members

We have preferentially hired people with overseas experiences and/or with an excellent command in English language. The TOEIC/TOEFL scores and particularly the writing and speaking abilities are considered as important factors for hiring. English language training sessions are conducted regularly for the staff members in the University and the staff members are encouraged to take them.

iv) Decision-making system

- Concretely describe the center's decision-making system.

In order to facilitate efficient and flexible administration of the research center, the Center Director has the sole authority of decision-making related to the personnel and management matters within the Center. The Center Director has the entire authority relating to the general management of the Center except for the removal of himself and the determination of his own salary. He has the authority over recruitment, hiring, contract renewal, salary, research space allocation, evaluation, and promotion regarding all Principal Investigators, visiting researchers, and post-doctoral fellows who are invited to the Center. He also has the right to make decisions on behalf of the Center, related to contracts with its Satellite institutes and the assignment and dismissal of researchers as the Center's Satellite Principal Investigators. In addition, he has the authority over the hiring and contract renewal of the Center's administrative staff members, excluding the full-time University staff members assigned to the Center by the University.

An external advisory board was planned initially to provide the Center Director with advice on the Center management, but it was realized that the working group for the Site Visit virtually serves as the external advisory board very well, giving many important advices. Due to budget constraints (especially unexpected reduction of the WPI subsidy from the initial plan), we have not organized the advisory board and taken advantages of having advices of the working group.

In order to facilitate center-wide discussions of administrative matters and personnel recruitment, the Center Director has created PI meetings and IIIS personnel committee, respectively. PI meetings are established to provide a periodic opportunity for PIs to openly discuss their opinions and concerns with the Center Director. The meetings are held once a month with video conferencing capability to allow satellite PIs outside of Japan to also attend and function as the steering committee within IIIS. The

personnel committee is chaired by the Center Director and comprised of 6 professors in related graduate schools and faculties in the University.

The Administrative Director supervises the administrative division and provides an environment where researchers can focus on their research. The PIs can make recommendations to the Center Director regarding the hiring of post-doctoral fellows and technical support staff members in the research laboratory he/she is supervising. Regardless of the position, anyone who is participating in this Center can offer his/her opinions regarding the management or treatment directly to the Center Director.

v) Allocation of authority between the center director and the host institution's side

- Concretely describe how authority is allocated between the center director and the host institution's side.

By positioning the research center as an independent research institute of the University, it is intended to assure a wide range of independent management, including personnel, facility management, and budget execution. As a result, under the strong leadership of the Center Director, a dynamic and prompt organizational management is enabled. Specifically, whereas the President of the University has the authority to elect or dismiss the Center Director, the Center Director has a wide range of authorities regarding the general management and internal administration of the research center. The Center Director has authorities over hiring, contract renewal, salary, allocation of research space, evaluation, and the promotion of the invited researchers, including PIs and post-doctoral fellows. He has the authority to hire and renew the administrative staff members, excluding the full-time staff members of the University assigned to the Center. This type of system is widely seen and most usual in the major universities and research institutes in the US, which would make the most of the Center Director's research and administrative experiences in the US. Moreover, the Center has established and maintains an intimate cooperation channel with the office of the President of the University and the Vice President in charge of research. When an important and legitimate issue arises regarding the management of the Center that requires amending or revising the current regulations and codes of the University, the President earnestly considers doing so through his top-down authority, while incessantly examining the system so that a prompt and flexible response is possible.

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

i) The "core" to be established within the host institution

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

	numbers		
	At beginning	At end of FY 2016	Final goal (March 31, 2022)
Researchers from within the host institution	7	8	8
Foreign researchers invited from abroad	0	6	6
Researchers invited from other Japanese institutions	0	8	10
Total principal investigators	7	22	24

- Describe the concrete plan to achieve final staffing goal, including steps and timetables.
- Attach a list of principal investigators using the Appendix. Place an asterisk (*) by names of the investigators considered to be ranked among the world's top researchers. Describe the policy and strategy for inviting the PIs who are to be included after 1 April 2017.

(At beginning)

The research center was inaugurated with the 7 existing faculty members of the University of Tsukuba (Masashi Yanagisawa, Hiromasa Funato, Ichiyo Matsuzaki, Hitoshi Shimano, Junichi Hayashi, Akiyoshi Fukamizu, and Satoru Takahashi) as Principal Investigators.

(At end of FY2016)

The Center invited Masanori Sakaguchi (RIKEN BSI) as a Jr. PI, Joseph Takahashi (UTSW) and Carla Green (UTSW) as Satellite PIs in FY 2012. In FY 2013, Takeshi Sakurai (Kanazawa Univ.), Hiroshi Nagase (Kitasato Univ.), Qunghua Liu (UTSW), Yoshihiro Urade (Osaka Bioscience Institute) and Robert Greene (UTSW), joined the Center as PIs, Michael Lazarus (Osaka Bioscience Institute), Yu Hayashi (RIKEN BSI) and Kaspar Vogt (Univ. of Basel) joined as Jr. PIs, Tetsuo Shimizu (Akita Univ.) joined as a Satellite PI. In addition, the Center invited Yang Dan (Univ. of California, Berkeley) as a Satellite PI in FY2014. Makoto Satoh (Univ. of Tsukuba) joined as PI, Kumpei Tokuyama (Univ. of Tsukuba) joined as a Collaborative PI and Hitoshi Okamura (Kyoto Univ.) joined as a Satellite PI, on the other hand, Junichi Hayashi retired on reaching retirement age in FY.2015.

(Final goal (circa March, 2022))

The inclusion of female PIs employment in the core group is crucial, and we continue our recruiting efforts to invite at least 2 female PIs promptly. We also consider promotion of female researchers to Jr. PI level. In addition, the Center has a possibility of coming in and out of PIs in prospect for its achievements as necessary.

b) Total members

	Numbers		
	At beginning	At end of FY 2016	Final goal (March 31, 2022)
Researchers	41 < 1; 2%> [8; 20%]	56 < 18; 32%> [17; 30%]	62 < 21; 34%> [22; 36%]
Principal investigators	7 < 1; 14%> [0; 0%]	22 < 8; 36%> [2; 9%]	24 < 8; 33%> [4; 17%]
Other researchers	34 < 0; 0 %> [8; 24 %]	34 < 10; 29%> [15; 44%]	38 < 13; 34%> [18; 47%]
Research support staffs	17	14	20
Graduate students	4	50	68
Administrative staffs (including secretaries for PIs)	14	19	19
Total number of people who form the "Core" of the research center	76	139	169

- Enter the total number of people in the columns above. In the "Researchers" column, put the number and percentage of overseas researchers in the < > brackets and the number and percentage of female researchers in the [] brackets.
- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing the main researchers, particularly principal investigators.

(At beginning)

The Center started with the 7 Principal Investigators from the University of Tsukuba and the members in their respective laboratories. Eighteen members joined from the FIRST program.

(At end of FY2016)

We successfully recruited a foreign (Indian) researcher in FY2012 and 4 foreign researchers (1 French, 1 German, 2 Canadians) in FY2013. Additionally, in FY2014 we hired 3 foreign researchers (1 Russian, 2 Indians), and also in FY2015 we hired 3 foreign researchers (2 Chinese, 1 British) including a postdoctoral researcher from our satellite in UTSW. The number of women among researchers in IIIS is steadily increasing, and the researchers excluding PIs, 15 (44%) are women.

In the research fields in which the Center engage actively, graduate students conducting bench works in the labs contribute significantly to PI's studies, and many PIs and other faculty members offer them on-the-job training in their labs. We thus include graduate students as a part of the list of total members above. In the University, the faculty organizations and the graduate schools are separated, and all faculties that would like to give lectures and to serve as official dissertation advisers have to be qualified by and registered in the graduate schools. All PIs in the Core group have been qualified for mentoring graduate students and accepted students from 4 graduate schools in the University.

(Final goal, March 2022)

We will employ 2 female PIs in the Core group and all post-doctoral fellows through international solicitations; highly talented young scientists will be recruited over the years. The Center will have approximately 60 researchers overall by the end of FY2021. Finally, the ratio of foreign and women researchers including PIs will be 34% and 36 % in FY2021, respectively.

ii) Collaboration with other institutions

- If the "core" forms linkages with other institutions, domestic and/or foreign, by establishing satellite functions, Provide the name of the partner institution(s), and describe the role of the satellite functions, personnel composition and structure, and collaborative framework between the host institution and the said partner institutions (e.g., contracts to be concluded, scheme for resource transfer).
- If some of the principal investigators will be stationed at satellites, attach a list of these principal investigators and the name of their satellite organizations using the Appendix.
- If the "core" forms organic linkages with other institutions, domestic and/or foreign, without establishing satellite functions, provide the names of the partner institutions and describe their roles and linkages within the center project.

[Satellite institutions]

1) University of Texas Southwestern Medical Center

A Satellite site has been installed at the University of Texas Southwestern Medical Center where the Center Director Masashi Yanagisawa conducted his research for over 20 years. As Satellite Principal Investigators, 4 world-leading researchers in the fields of circadian rhythm, sleep, and siRNA, Joseph Takahashi, Carla Green, Robby Greene and Qinghua Liu have participated. A total of three WPI-funded post-doctoral fellows are hired for these laboratories. A close collaboration with the Takahashi laboratory has been ongoing for over seven years already, concerning the mouse forward genetics project. His continued contributions are essential in order to carry through the project. The presence of these Satellite PIs further elevates the global visibility of this WPI Center.

2) Akita University

We have established a Satellite at the Akita University, which is by far Japan's largest site for patient-based clinical studies on the orexin system. The Satellite Principal Investigator, Tetsuo Shimizu, is a professor of the Department of Neuropsychiatry, and has an extensive network of patients and medical institutions for clinical research of sleep disorders including narcolepsy. We also facilitate a human molecular genetic study of short sleepers in this collaboration.

3) University of California, Berkeley

We recruited Yang Dan as Satellite PI in FY2014 to engage in joint research into the analysis of intracerebral neural circuits of sleep-awake control. We have tied-up while developing analytical technology such as the optrode method, etc. to demonstrate power in analyzing nerve cell network.

4) Graduate School of Pharmaceutical Sciences, Kyoto University

We installed Hitoshi Okamura, the Department of System Biology, Kyoto University Graduate School of Pharmaceutical Sciences as Satellite PI in FY2015. The objective of this collaboration is to fish out genes regulating jet-lag by ENU mutagenesis screening.

5) Merck Sharp and Dohme (MSD)

We started the joint research project with MSD from FY2015. Dr. John Renger, Associate Vice President, Target Acceleration and Translation, Neuroscience was assigned as IIS Satellite PI. Unfortunately, he has left MSD recently, and his successor will take over the position.

In order to facilitate the progress of research based on intimate interactions between the Tsukuba Core and the Satellite sites, we have periodical internet-based video conferences. Also, these Satellite Principal Investigators and the Center Director will regularly visit each other in person.

[Partner institutions]

- 1) RIKEN BioResource Center, Tsukuba
We closely collaborated with Dr. Shigeharu Wakana and his team in our forward genetic screening and mapping of sleep/wake mutant mice, which was a major pillar of the FIRST project. We continue the collaboration with RIKEN BioResource Center as a partner institution for systematic mouse phenotyping.
- 2) RIKEN Brain Science Institute
We conduct joint research with Dr. Shigeyoshi Itohara of the RIKEN Brain Science Institute, Laboratory for Behavioral Genetics, on the study to elucidate the physiological significance of sleep toward developing therapy for mental disorders.
- 3) Ibaraki Prefecture/Ibaraki Prefectural Medical Center of Psychiatry
We conduct a joint project with the Hospital Management Division of Ibaraki Prefecture intended to promote clinical research into sleep disorders (sleep apnea syndrome in particular).
- 4) Center for Genomic Medicine, Kyoto University
We collaborate with Dr. Fumihiko Matsuda, the Center for Genomic Medicine, Kyoto University to commence joint research to bridge our mouse forward genetics to a human genome epidemiological study, as a part of our translational research.
- 5) JAXA Space Biomedical Research Office
We conduct a basic study to develop an automated sleep diagnosis system, and evaluate safety of insomnia treatment drugs in the collaboration with JAXA. We also join the closed-environment stress test to be conducted in the isolation/confinement facility in JAXA, studying effect of the stress on sleep.

5. Research Environment

• Concretely describe measures to be taken to satisfy each of the requirements outlined below, including steps and timetables.

- i) **Provide an environment in which researchers can devote themselves exclusively to their research, by exempting them from other duties and providing them with adequate staff support to handle paperwork and other administrative functions.**

1. Support by administrative division

We have implemented an administrative support system that reduces the burden of administrative obligations of researchers and allows them to devote themselves exclusively to their research. Our administrative team promptly respond to the intentions of the Center Director. Under the supervision of the Administrative Director who has a thorough knowledge in both the science research and the management affairs of pharmaceutical industries, the administrative division functions autonomously and independently from the University administration. Specifically, the administrative division fully and promptly performs any necessary support for the conduct of research, including legal affairs, general affairs, personnel affairs, employment, business travel, work management, public relations (outreach activities), symposia, conferences, overseas alliance, research alliance, acceptance of overseas personnel, budget management and execution, procurement, domestic and overseas transfer of funds and supplies, as well as the tasks related to competitive research funds, including information collection, application support, project management and support for report preparations and management for safety and hygiene.

We allocate Ph.D. scientists to the key positions in the administration to act as an interface between researchers (the Center Director and PIs) and the administrative staffs without scientific background in the administration, and assign the University Research Administrator (URA) from the URA Support Office of the university headquarters to the project manager for joint research projects to secure good communication and smooth implementation of respective projects.

2. Living support

The University of Tsukuba promotes “Globalization as a matter of daily living” as one of the institutions that have been selected as a core university of the “Global 30” sponsored by the Ministry of Education, Culture, Sports, Science and Technology (MEXT). On campus, Global Commons, International Exchange Support Office, provides livelihood support and services for foreign researchers and their families including Japanese classes. In addition, the university guesthouses and its affiliated housings nearby are available for researchers (especially foreigners), administrative staff members and their families. We continue the contract with Japan International Science and Technology Exchange Center (JISTEC) which provides a wide range of living support as well as living accommodation for researchers from foreign countries. In collaboration with JISTEC, the Center provides various supports, including visa application, paperwork such as alien registration at City Hall, opening bank account, purchasing insurance, and arranging for residence.

ii) Provide startup research funding as necessary to ensure that top-caliber researchers invited to the center do not upon arrival lose momentum in vigorously pursuing their work out of concern over the need to apply immediately for competitive grants.

For the independent researchers who were recruited to the Tsukuba Core from other institutions (especially those from overseas institutions), the Center provided a sufficient amount of startup research funding especially in the first two years to build necessary infrastructures and set up facilities and equipment. The plan of the funds was drafted by the Administrative Director and implemented based on the budget plan decided by the Center Director. Since FY2014, an Internal Grant system has been introduced as start-up funding, especially for researchers who failed to acquire competitive funds such as Grants-in-aid for Scientific Research, etc. Applications with a research plan were collected within IIS and screened by the faculty staff in the administrative department to secure fair and unbiased review. For the application of external funding, the administrative division provides PIs with strong supports through the entire application process.

iii) As a rule, fill postdoctoral positions through open international solicitations.

In order for the Center to survive and stand out as an outstanding research center after 10 years, it is imperative to recruit excellent young talents. International recruitment has been conducted by using the following means to hire outstanding post-doctoral fellows.

1. Prominent international journals such as *Nature* and *Science*; 2. Personnel database JREC-IN (Japan Research Career Information Network) operated by the Japan Science and Technology Agency; 3. Web sites of academic research societies such as the Japan Neuroscience Society; 4. University of Tsukuba web site (in four languages); 5. Departmental web sites; 6. University of Tsukuba's overseas offices; 7. Our overseas Satellite (public release by the University of Texas Southwestern Medical Center), So far the Center has received 392 applications for the postdoctoral positions, demonstrating it has attracted a lot of attentions by young talents. Apart from those, we continuously conduct recruitment through personal international networks of the Center Director and PIs as well as contacts at various opportunities such as the symposium hosted by IIS and international conferences of the respective academic societies.

The University of Tsukuba is equipped with various career and living support systems for the development of young researchers at all levels. By utilizing such systems, we are aggressively promoting the participation of outstanding post-doctoral fellows, especially foreign researchers and female scientists.

The Center Director strives to create an environment that attracts quality personnel by aggressively outreaching to society, thereby increasing the visibility of the research center.

The young researchers working at the Center strive to achieve research accomplishments sufficiently high so that they will then be recruited by other institutions for the next career stage. This would promote healthy personnel mobility, ultimately helping the Center to sustain its world premier status.

iv) Establish English as the primary language for work-related communication, and appoint administrative personnel who can facilitate the use of English in the work process.

Needless to say, all science is conducted in English at the Center. In addition, all administrative staff members are fluent in spoken and written English, except for the people who have specific skills that cannot be replaced by any other people. Documentation is in English or bilingual as much as possible, except where it has to be in Japanese for external reasons.

The TOEIC/TOEFL scores and particularly the writing and speaking abilities are considered as important factors when appointing administrative personnel. English language training sessions are conducted regularly for the staff members.

- v) **Adopt a rigorous system for evaluating research and a system of merit-based compensation. (For example, institute a merit-based annual salary system primarily for researchers from outside the host institution. As a basic rule, the salaries of researchers who were already employed at the host institution prior to the centers' establishment are to be paid by the host institution.)**

The President of the University decides on the renewal and the salary of the Center Director.

The Principal Investigators and other independent researchers are annually evaluated by the Center Director, considering their achievements. 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, has been established. We are thus considering the index as an evaluation tool to build a system of merit-based compensation. The Center Director decides on the salaries of the Principal Investigators and other independent researchers considering the results of the annual evaluations.

The salaries of the other researchers and administrative staff members are decided by the Center Director based on the opinions of the supervising investigator and Administrative Director, respectively. The index mentioned above could be also used for the evaluation tool for the other researchers.

When inviting Principal Investigators and other independent investigators from outside of the host institution, their salaries are determined according to their research accomplishments and previous salaries.

- vi) **Provide equipment and facilities, including laboratory space, appropriate to a top world-level research center.**

The Center has been provided with a sufficient amount of floor space that can be favorably compared, on a per-capita basis, with the floor spaces of premier research centers in the U.S. These include wet-lab spaces, dry-lab/office spaces, and animal housing spaces especially for mice. Generous space for animal housing is absolutely essential considering the Center's target research field.

Specifically, construction of a new building to house the Center is being planned. The construction will start in FY2013 and completed by the end of FY2014.

The design of the new research building was completed in Nov 2013, construction started in Feb 2014, and construction of the major part (6,000 m²) supported by the MEXT subsidy completed in Mar 2015. Subsequently, construction of the additional part covered by in-house funding was completed, and IIS Building with 6 stories, total floor space of 8,000 m² (including 2,000 m² self-funded) was completed in June 2015. Relocation was completed in Aug 2015, and laboratories that were scattered around the university campus are now under the same roof, to form the leading global research center of sleep science covering the scope from molecular genetics, neuroscience, pharmaceutical science, clinical sleep physiology, and to experimental medicine. In Mar 2016, landscaping including the parking lots for 100 cars was also completed. One of the most distinctive features of the building is the animal breeding/experimental areas, which require high levels of cleanliness and security, are located on the upper floors (5, 6F). These areas are comprised of clean rooms with state-of-the-art air conditioning

system featuring airtight barriers established with room pressures controlled section by section, as well as individually configurable temperature and humidity. The breeding area on the sixth floor includes the cleaning and sterilization room with two large autoclaves and a rack washer, and breeding rooms with an automated water feeder, RO (reverse osmosis membrane) water-purifying apparatus and a device for producing weakly acidic sterilizing water, which can accommodate up to 6,000 IVC cages for mice/rats, capable of breeding tens of thousands of the same. The experimental area on the fifth floor also includes seven sleep recording rooms and six behavioral labs with the equipment for sleep/behavior analysis. In future, the numbers of racks and cages will be increased and the breeding capability reinforced in accordance with research development. In addition to the existing shared capital devices such as a large-scale mouse electroencephalograph system, cutting-edge shared devices, e.g., a fiber-optic fluorescence confocal microscope, a high-resolution mass spectrometer (Orbitrap Fusion), 3D micro X-ray CTs for experimental animals (R_mCT2-SP), bioluminescent/ fluorescent *in vivo* imaging system (IVIS) for small animals, multiphoton excitation imaging systems (Zeiss Axio), FACS (BD 4LS), and slide scanners (NanoZoomer-XR), have been systematically acquired in the Center, according to the requirements of its laboratories.

To develop a clinical sleep lab, a human metabolic chamber with a bed for clinical research and an organic EL lighting system will be installed on the 3rd floor of the building soon. In the next few years, we aim at implementation of the future expansion space on the south side of the 4th floor in the building. Potential usages include an open-innovation drug discovery lab sponsored by pharmaceutical companies and hosting a research group for the JST basic research programs.

vii) Hold international research conferences or symposiums regularly (at least once a year) to bring the world's leading researchers together at the center.

The Center Director served as the organizer of the 5 international symposia every year since IIIS was established in 2012. All of those symposia were conducted in English including oral and poster presentations, and gathered more than 150 audiences every time.

In order to create a "globally visible research center", we will keep regularly holding similar symposia once a year, and invited seminar series twice a month. Providing workshops at overseas Satellites will also increase the visibility of the research center overseas.

viii) Other measures to ensure that top-caliber researchers from around the world can comfortably devote themselves to their research in a competitive international environment, if any.

The University Research Administrator (URA) office of the University of Tsukuba (director: vice president in charge of research), which has been established as a part of the "Global 30" initiative by the MEXT, provides the Center with additional know-how on development strategies, international cooperation, and compliance by dispatching a URA to the Center.

The IIIS Building was carefully designed to provide the researchers with collegiate environments. Centering around an open ceiling space with a symbolic spiral staircase linking floors one to four, lab offices, lounges and auditorium are arranged in migratory fashion, so that researchers can naturally meet, interact and influence each other to further boost intelligent inspiration from various disciplines and fields of research and accelerate the fusion research. Five formative art works created by the joint project with artists in Faculty of Art and Design, University of Tsukuba are arranged/exhibited at each location in the building to stimulate the intellectual curiosity of researchers and symbolize the fusion. The spacious wood deck projecting toward the pond and the promenade running along the same around the research building are venues for researchers to relax and interact.

6. Indicators for evaluating a center's global standing

• Describe concretely the following points.

i) Criteria and methods to be used for evaluating the center's global standing in the subject field

1. Number of citations of published papers in the medium to long term
The degree of scientific contribution of research work is sensitively reflected upon the number of citations in the medium to long term.
2. Positions and scientific accomplishments of the alumni (trainee) of the research center
When evaluating a research center in the US, positions that previous graduate students and post-doctoral fellows acquire in the following years become an important evaluation index.
3. Funding
Since it is a reflection of the quality of the research plan and previous performances and contributions, funding is an important evaluation index.

ii) Results of current assessment made using said criteria and methods

1. As for the Center Director's work, the number of citations for the article that reported the discovery of orexins is 4,264 and for the article describing narcolepsy episodes in orexin-deficient mice, the number of citations are 2,515 (as of February 1, 2017). These high numbers of citations suggest that these articles are remarkable reports that greatly affected research activities of other researchers in the field.
2. Many researchers who received trainings from Masashi Yanagisawa as post-doctoral fellows have become professors and assistant professors of domestic and overseas universities, working in responsible positions in research institutions and corporate settings. The value of such personnel network is very immense. Such real examples are attracting excellent graduate students and post-doctoral fellows to this research center.

iii) Goals to be achieved through the project (at time of final evaluation)

1. The citation indices of our publications surpass those at other premier research centers for sleep science, such as the Stanford Center for Sleep Sciences and Medicine.
2. More senior alumni of the research center have attained independent positions in the academia and in the industry, both domestic and overseas.
3. Maintain the level of research grant acquisition.

7. Securing research funding

Future prospects

- Describe the concrete prospects for securing resources that match or exceed the project grant.
- Calculate the total amount of research funding (e.g., competitive funding) based on the percentage of time the researchers devote to research activities at the center vis-à-vis the total time they spend conducting research activities. Be sure the prospects are realistically based on the past record.

i) Past record

FY2012: \$4,534,400 (FIRST \$4,519,200, other external funds \$ 15,200)
 FY 2013: \$4,614,600 (FIRST \$3,976,200, other external funds \$ 638,400)
 FY 2014: \$1,779,300 (FIRST \$ 0, other external funds \$1,779,300)
 FY 2015: \$2,820,700 (FIRST \$ 0, other external funds \$2,820,700)
 FY 2016: \$6,102,800 (FIRST \$ 0, other external funds \$6,102,800)
 (Exchange rate for 1 US Dollar = 100 yen)

The total amount of competitive research funding raised by the Principal Investigators in the past five years is \$19,851,800 averaging at \$3,970,400/year.

ii) Prospects in the second half of the WPI program period

The University of Tsukuba is responsible for the labor costs for the vice center director (93% by the

combined wage system), the 5 Collaborative PIs who were full-time faculties at the University before participating in this research center, and for the 3 full-time University staffs who are appointed to the administrative division of this research center. The University supported 1.8 billion yen for the costs of new research building, facilities, equipment, exterior, landscaping including a parking lot and moving from temporary labs distributed among 4 places in the university campus. In addition to the personnel expenses mentioned above, light, heating and water utility costs of the IIIS Building are spent by the University as a major financial support for the operation of the Center.

The Center Director resigned from Howard Hughes Medical Institute (HHMI) Investigator according to recommendation by the WPI committee, and the significant funding from HHMI was lost at the end of FY2013. After the completion in FY2014 of the FIRST program that founded this center, the total amount of competitive funds dropped to a level of serious concerns, i.e., 1.78 million US\$, but the financial crisis was avoided quickly by rapid increases in the external funds growing by 100% every year. The amount in FY2016 reached 6.10 million US\$ thanks to great efforts by all researchers participating in the Core Team of the Center. Applications for other large-scale research grants are still in progress. Considering the level of competitive research funds acquired by the PIs in the recent past, we expect that we will be able to secure about the same level of research funds or more after FY2017.

Others

- Describe activities and initiatives to be taken after project funding ends.
- Describe expected ripple effects (e.g., how the research center project will have trailblazing components that can be referred to by other departments in the host institution and/or other research institutions when attempting to build their own top world-level research centers).
- Describe other important measures to be taken in creating a world premier international research center, if any.

After the end of this funding, the University will maintain the research center as a permanent organization. Administrative procedures that are required for the establishment of a formal research institute will be completed in a few years. By the end of this funding, the procedures necessary for the stable operation of the research center even after the end of the program will be complete, such as offering a tenure position to the multiple Principal Investigators that produces sufficient research achievements.

As for the "ripple effects," we believe that the concept of creating at Tsukuba an organization, which is akin to small "departments" in the US universities, as described in the Center Director's vision, has a significant impact on other organizations in Tsukuba and elsewhere. Specifically, (i) the number of faculty positions is never fixed in advance; when an outstanding faculty candidate is identified, the Center Director has the authority to allocate the institutional and other funds in order to hire him or her in a timely and flexible fashion. (ii) The Principal Investigator's salary level would be individually negotiated by the Center Director, considering the recruiting situations and his/her prior salary levels, and in accordance of broad guidelines of the institution. (iii) The floor space for each laboratory within IIIS would be allocated flexibly and dynamically, considering the laboratory's scale of funding, number of personnel, and facility requirements. (iv) A researcher who is deemed capable of conducting scientifically independent research would be provided with an appropriate position as an immediately independent scientist (who would publish his/her studies as the corresponding senior author), together with a necessary startup package. (v) Regardless of their age or career stage, all scientists in IIIS should freely discuss science with each other, constantly seeking for opportunities for formal and informal cooperation.

Center Director's Vision

Chief center-project officer/Center director
Masashi Yanagisawa,
Center for Behavioral Molecular Genetics, Professor

- Background, Targets and Objectives

We spend one third of our life in sleep, a behavioral state observed ubiquitously in all mammals and other animal species with well-developed brains, even including fish and insects. Indeed, sleep is the only physiological state in which a healthy individual reversibly loses consciousness, posing a great evolutionary risk of being completely vulnerable and unproductive. Amazingly, however, the fundamental function of sleep remains unknown. In today's society, disorder of sleep is not only a major problem in itself, but a well-recognized risk factor for lifestyle diseases such as the metabolic syndrome and mental diseases such as mood disorders. Sleep disturbances can also manifest as a difficult symptom in various neurological and psychiatric conditions such as dementia and depression. However, because we know very little about the fundamental mechanisms for sleep regulation, we have very few means of medical intervention for sleep disturbances. For example, a majority of sleep pills available today all share a single mechanism of action, i.e. facilitation of the GABA-A receptor. It also remains utterly unknown how sleep disturbances lead to metabolic dysregulations such as insulin resistance.

Our discovery of the neuropeptide orexin and its prominent role in sleep/wakefulness regulation has generated a highly active research field in the neurobiology of sleep and metabolism (our two Cell papers have been cited for >4,300 times combined). Triggered in part by our discoveries, the downstream, executive neural circuitry and chemistry for the "sleep/wake switch" has been increasingly revealed in recent years. However, the fundamental governing principle for the regulation of sleep pressure, i.e., the question of what is the neural substrate for "sleepiness," whether or not it is localized in the brain, and how it is ultimately regulated, remains a mystery. Well-described is the phenomenological aspects of sleepiness, with at least three distinct modalities of regulation: i) the circadian regulation by the internal clock of our brain (sleepiness due to jet lag); ii) the homeostatic regulation by the history of sleep amounts in the recent past (sleepiness after sitting up all night); and iii) the emotive regulation of arousal (sleepiness forgotten when excited or in emergency). Precise details in the molecular machinery of circadian clocks have been uncovered through intensive research efforts triggered by the pioneering body of work by Professor Joseph Takahashi (the proposed head of the U.S. Satellite site in this WPI) and others. However, the neuronal pathways through which the master clock in the

suprachiasmatic nucleus can eventually regulate sleepiness remain unknown. Even more frustrating is the fact that the mechanism for sleep homeostasis remains as one of the biggest black boxes of today's neuroscience, despite the fact that, phenomenally, it appears to be a deceptively simple negative-feedback system.

I have been convinced that new, highly interdisciplinary approaches are absolutely required in order to crack open the black box of sleep regulation, and in order to develop truly new means for controlling sleep and treating sleep disorders. The present proposal originates from this conviction, which I have attained through more than a decade of intensive studies since our discovery of orexin. In 2009, I was selected as one of the Principal Investigators for the FIRST research program funded by the Cabinet Office of Japan, which helped me setting up a new research core at the University of Tsukuba focusing on sleep neurobiology, while simultaneously retaining my position at the University of Texas Southwestern Medical Center (UTSW) and the Howard Hughes Medical Institute (HHMI). Already ongoing in this FIRST program are intensive interdisciplinary collaborations spanning such diverse fields as forward genetics, optical neurophysiology and medicinal chemistry. Many of the proposed PIs in the present application are these collaborators through the FIRST program, including Joseph Takahashi (UTSW/HHMI), Takeshi Sakurai (Kanazawa University), Hiroshi Nagase (Kitasato University), and Satoru Takahashi (University of Tsukuba).

Under this FIRST program, we are currently carrying out a number of ambitious, long-term projects, including: (1) Large-scale forward genetic screening of randomly mutagenized mice for sleep/wake abnormalities (collaboration with Takahashi, J. and Takahashi, S.). We have so far screened ~4,000 mutagenized mice by conducting electroencephalography-based sleep analysis on each mouse, and detected at least 4 pedigrees of mice exhibiting marked, heritable abnormalities of sleep/wake patterns. We are now identifying the causative mutations by SNP-based linkage analysis and whole-exome sequencing. (2) Development of new drug candidates that target orexin receptors (collaboration with Nagase). At UTSW, we have screened a library of 250,000 drug-like compounds, and identified several distinct chemical classes of compounds acting as specific orexin receptor agonists. Some of them are found to penetrate the blood-brain barrier. Medicinal chemistry efforts are ongoing in order to further optimize these agonists. (3) Real-time visualization in freely behaving mice of activity patterns of specific neuronal populations involved in sleep/wake regulation, such as orexin neurons (collaboration with Sakurai). We are pursuing several different optical and electrophysiological approaches, including the use of a newly developed, fiber-optic fluorescence endo-microscopy in order to visualize the activity of specific populations of neurons located in deep brain structures such as the hypothalamus. We have already succeeded in optically visualizing the activity of some of these deep-brain neurons involved in sleep/wake regulation.

The present WPI proposal bases itself upon our ongoing FIRST program. While focusing sharply on the “biomedicine of sleep” as target problem, it will gather top researchers from a wide range of fields spanning from neurobiology to medicinal chemistry to clinical-social medicine. By doing so, it will create a new type of research center at Tsukuba, which is highly visible internationally and sustainable for long term. If it is funded, I will fully return to Japan and work full time at Tsukuba as the Center Director. As for its Principal Investigators, in addition to the seven University of Tsukuba scientists who are internationally recognized for their work that are closely related to the present objective, we will recruit a number of top scientists to Tsukuba from the U.S. and from within Japan. The proposal will create a U.S. Satellite site at UTSW, with the prominent local Principal Investigators whom I have already been closely collaborating with. My own 20-year tenure at UTSW will be fully utilized in order to maintain and further our close cooperation. Out of the 12 Principal Investigators who will be working at the Tsukuba site, three will be foreigners including myself (I am a naturalized U.S. citizen). Including the Satellite sites, 5 out of the 15 proposed Principal Investigators will be foreigners.

- Creating a new style of research center at Tsukuba by learning from the merits and virtues in the organization of “departments” in major U.S. universities.

I have had a plenty of opportunities to learn about the merits and demerits of U.S.-style research organizations and systems. This has been through my 20-year tenure as a professor at UTSW, one of the best biomedical campuses in the U.S., where I have been working also as an HHMI Investigator and serving as an elected member of the National Academy of Sciences. I believe that we can implement the WPI’s mission and mandate aiming at “system reform” by selectively learning from the merits of departmental organizations and systems in the U.S. academia. For example, departments would not set fixed a priori the total number of its tenure-track / tenured professors and other faculty members (e.g., research-track professors); when an outstanding faculty candidate is identified, the chairman has the authority to allocate the departmental and other funds in order to hire him or her in a timely and flexible fashion. Selecting and recruiting a faculty candidate would eventually be done through the authority of the chairman, often being helped by a departmental recruiting committee, although the decisions would be made only after thorough discussions among the faculty members of the department as well as consultations with important researchers outside the department. The researcher’s salary level would be individually negotiated by the chairman, considering the recruiting situations and his/her prior salary levels, and in accordance of broad guidelines of the institution. The floor space for each laboratory within the department would be allocated flexibly and dynamically, considering the laboratory’s scale of funding, number of personnel, and facility requirements. Capital equipment and large facilities would be shared among the laboratories as

much as practically possible. Supported by the strong commitment from the President's Office of the University of Tsukuba, I will aggressively implement these practices, which may sound quite usual in the U.S. but not necessarily so in Japan.

One important characteristic of individual laboratories in the U.S. academic departments is a relatively flat hierarchy among the laboratory members: usually, there are only two levels (principal investigator / others) or three levels at most (principal investigator / research faculty or senior postdoc / others). In the proposed Center, I will incorporate these flat personnel structures, especially in order to encourage and develop young independent researchers. Whenever we identify a post-doctoral scientist who is deemed capable of conducting scientifically independent research, we will provide him or her with an appropriate position as an independent scientist (who would publish his/her studies as the corresponding senior author), together with a necessary startup package. Our proposal includes a generous amount of fund set aside for this purpose. Regardless of their age or career stage, all scientists in our Center will freely discuss science with each other, constantly seeking for opportunities for formal and informal cooperation.

- Fusion of neuroscience and medicinal chemistry

One of the important missions of WPI-Focus is to create new paradigm of research by the fusion of traditionally separate fields. One such fusion-driven modality that has been getting a lot of attention in the U.S. in recent years is often called "chemical genetics" or "chemical biology." Even though Japan's tradition of synthetic organic chemistry excels globally with its breadth and depth, highly practical aspects of medicinal chemistry has long been considered in Japan an exclusive domain for the pharmaceutical industry. Never popular in Japan until very recently has been the idea of carrying out everything in the academia, from high-throughput screening of large-scale compound libraries to medicinal chemistry efforts of optimizing hit compounds, while conducting various *in vivo* and *in vitro* assays. The department where I work at UTSW is, in fact, among the very first academic sites to implement serious chemical biology capabilities. It boasts not only a high-quality, diversity-optimized library of drug-like compounds with sophisticated screening robotics, but also a panel of 6-7 expert medicinal chemists as full-time professors, some of whom recruited from the industry.

In the present WPI proposal, I will recruit our FIRST collaborator Professor Hiroshi Nagase from Kitasato University to Tsukuba, in order to forcefully propel a fusion of neurogenetics/physiology and medicinal chemistry. Through his career, Professor Nagase has created not one but two first-in-class, marketed drug compounds (an orally-active prostacyclin analogue and a kappa-selective opioid receptor agonist) -- indeed, a rare achievement as a medicinal chemist. In the proposed WPI Center,

multiple efforts of serious and practical medicinal chemistry will be spread out from Professor Nagase's laboratory as a core.

- Continuing to provide a research environment and culture where scientists are encouraged to take “calculated scientific risks”

I am firmly convinced from my own past experiences that truly valuable discoveries cannot be achieved without taking “calculated risks” in the course of research. In my view, in order to take a calculated scientific risk, a scientist has to carefully consider the resources available to him/her, incorporate the cutting-edge methodologies of the day, and have the “technical courage” of switching the field if necessary. It is a bitter truth of today's scientific world that one often has to carry out some lower-risk studies in order to survive as a professional scientist. However, I believe that our WPI Center has to keep providing a scientific culture and environment that strongly encourages all its members, regardless of career stage, to take calculated risks and initiate “truly interesting” studies.

One example of practical methods to provide such an environment is to facilitate networking with outside researchers by organizing a regular departmental seminar series. Having regular, frequent seminars by prominent scientists invited from other institutions is, in my opinion, a salient feature of the departmental system in major U.S. universities. I have never seen a major academic department in the U.S. that does not organize a regular departmental seminar series; many larger departments host weekly seminars. I observe that, unfortunately, such seminars by outside scientists are much fewer and held only irregularly even in largest universities in Japan. In other words, scientists in Japan pay “seminar visits” to other campuses much less frequently in general. Importantly, during such visits, the invited speaker would personally meet with many local faculty members, often including some from unrelated field. The present proposal takes this problem seriously; we will organize and host a regular (at least biweekly) seminar series, inviting scientists working in broadly related fields from within Japan and from abroad. It is obvious that this will also facilitate the aforementioned training of young scientists to be independent at early stage, as well as the aforementioned fusion of distinct fields of research. In the end, the proposed Center will aim at providing each independent scientist sufficient initial resources, as well as support and environment for obtaining further external resources, so that his/her own scientific ideas are the only bottleneck of research.

- Contributing to the Society

Sound sleep is essential for physical and mental health; deficiencies in the amount and quality of sleep will lead not only to a decrease in higher cognitive functions of the brain including memory and decision making, but also to an elevated risk for

mood disorders such as depression. It is alarming that the lifetime prevalence of sleep disorders exceeds 30% in industrialized countries. Nocturnal lifestyle of today's society, shift-workers amounting to more than 20% of working population, and steady increase of elderly population all contribute to the problem. Social loss attributable to sleep disorders is significant, including automotive accidents due to excessive sleepiness, increase in the prevalence of mood disorders, increase in suicide, and increase in wandering and delirium in elderly patients leading to excessive loads on caretakers. An ultimate goal of the present proposal is development of new methods for intervening in sleep disturbances and related disorders based on discoveries in the basic research, thereby responding to needs of the society. In order to achieve this, I believe that an aggressive effort for societal outreach is also essential.

- Concluding remark

I believe that my own mission under this proposal can be summarized as follows: Fully return to Japan as a full-time Center Director, and create a new "departmental" site for premiere sleep research at Tsukuba, by learning from the merits of the U.S.-style academic systems and organizations while retaining the merits of the Japanese tradition (such as the attitude to patiently support long-term projects), which can only be achieved by fully utilizing over 20 years of my experience as a principal investigator in the U.S. academia.

Host Institution's Commitment (in English)

February 20, 2017

To MEXT

Name of host institution University of Tsukuba
Name and title of head of host institution Kyosuke NAGATA, President

Signature by _____
Kyosuke Nagata
President
University of Tsukuba, Japan

I confirm that the measures listed below has been taken faithfully since the "International Institute for Integrative Sleep Medicine" was adopted under the World Premier International Research Center Initiative in 2012.

<Provision in host institution's mid-to-long-term plan>

•Describe clearly the host institution's mid-to-long-term strategy plan and how the center is positioned within that strategy.

In University of Tsukuba's Midterm Goals (for the period of April 2010 to March 2016), it is proclaimed that the University shall "strive for deeply specialized expertise, open up new cross-disciplinary fields, and achieve research results which are outstanding by international standards over a wide range of academic fields."

In the University's Midterm Plan to reach these goals, it is stated that the University shall "promote high quality fundamental research taking a long term view of academic progress and ambitiously open up new cross-disciplinary fields," and "under the leadership of the President carry out research intensively in fields where the University has distinctive capabilities, in particular those which are internationally recognized to have great potential and budding new fields which invite the interaction of existing fields."

Therefore, the World Premier International Research Center Initiative (WPI) is in complete agreement with the University's Midterm Goals and Midterm Plan.

Further, as the strategy to achieve the University's goals regarding systems to carry out research, the Midterm Plan stipulates that "research groups and organizations which are expected to achieve outstanding research results will be singled out for appropriate support, including allocation of research resources, hiring of supporting personnel, and reforming of organizations, and will be aggressively promoted as international centers of research."

In accordance with this Midterm Plan, these research centers have been given the highest priority in the University's development efforts. In particular, under the leadership of the President, a deliberative committee preparing for the establishment of the University of Tsukuba International Institute for Integrative Sleep Medicine had been launched. The whole University was involved to make the level of work at this international research center on par with any center in the world.

The first of the Midterm Goals is to make this an "open university" in every aspect, with a "flexible educational and research organization" that is not tied down by past conceptions and that will take the lead in promoting "new ventures for the university" that are called for by tomorrow's society.

Center director Dr. Masashi Yanagisawa, had been a professor at the University of Texas for over

20 years, and uses this experience in managing this center. By incessantly supporting his efforts, the University is realizing the “new ventures for the university” that are demanded by tomorrow’s society.

We specified “International Institute for Integrative Sleep Medicine” for a Midterm Plan in FY2012.

<Concrete Measures>

·Describe the concrete measures that the host institution will take to satisfy the following requirements.

(1) How it will support the center’s need to secure resources that match or exceed the project grant through such means as competitive grants obtained by researchers participating in the project, in-kind contributions and other forms of assistance by the host institution (including partial payment of salaries, provision of research space), and/or external donations.

In order to manage this center and carry out research activities there, the University is giving support as indicated below which amounts to at least as much as the support supplied by the WPI program. Further, even after the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program) ends its “Molecular Mechanism and Control of Complex Behaviors” project which formed the basis of this center, personnel and laboratory resources have been expanded significantly through MEXT’s kind support as well as the University’s self-funding and outside funding to support the participating researchers.

- 1) The University of Tsukuba Organization for the Support and Development of Strategic Initiatives (formed by the University President and Vice-President) continues to give intensive support to make this an international center pioneering new fields, as one of the Organization’s strategic initiatives. Specifically, the Organization supports the center with ¥10 million per year to cover expenses of center activities.
- 2) Competitive research funds obtained by researchers participating in the center
Competitive research funds obtained by researchers participating in the center amounted to an average of US\$8.86 million in the past 5 years, and it was anticipated that an equivalent amount would be gained. However, the Center Director resigned from Howard Hughes Medical Institute (HHMI) Investigator according to recommendation by the WPI committee, and the significant funding from HHMI was lost at the end of FY2013. After the completion in FY2014 of the FIRST program that founded this center, the total amount of competitive funds dropped to a level of serious concerns, i.e., US\$1.78 million, but the financial crisis was avoided quickly by rapid increases in the external funds growing by 100% every year. The amount in FY2016 reached US\$6.10 million thanks to great efforts by all researchers participating in this center. The University has provided full support for their applications for competitive external and internal research funds.
- 3) Support through handling of personnel expenses
The personnel expenses of the Vice Center Director and 5 Collaborative PIs in the University participating in this center have been treated as University personnel expenses for researchers. University staffs (3 persons) have been assigned to carry out the administrative works of the center such as general affairs and accounting. The expenses for these staff have been handled by considering them to be administrative staff participating in an administrative support division. Further, a half of personnel expenses of a University Research Administrator has been born by the University.
- 4) Support through supply of research space
The University used its Facility Department to implement building of research facilities (8,000 m²) according to a plan that gives the center an outstanding research environment and distinctive tangible advantages.
- 5) Support for the use of research facilities
Various core facilities have been offered for use (see paragraph (5) below).

(2) How it will institute a system under which the center’s director is able to make substantive personnel and budget allocation decisions necessary to implementing the center project—a system, which in practice, allows the center director autonomy in making decisions regarding the center’s operation.

This center is established as an independent research organization separate from other research bodies, and also as a special institute for the purpose of making the level of research at the center as high as any in the world.

In order for the center director to be able to fully exercise his leadership, the system has been instituted in which the director has managerial powers over key aspects of the center, including the power to decide upon personnel and the budget. In order to implement this system, the University has taken necessary measures such as amending relevant regulations as needed. Further, the director is supported by the administrative division established within this center which includes Professor Toshio Kokubo who has rich administrative experience such as the Senior Director of Biomedical Research Laboratories, Pharmaceutical Division, Takeda Pharmaceutical Co. Ltd., administrative personnel dispatched from the University for support, and other personnel recruited from outside the University. These personnel supply the director with the information needed for him to hand down decisions, and keep the director’s work load from becoming excessive.

(3) The support it will provide to the center director in coordinating with other departments within the host institution when recruiting researchers for the center, while giving reasonable regard to the educational and research activities of those departments.

The Deliberative Committee to Prepare for Establishment of the University of Tsukuba International Institute for Integrative Sleep Medicine was established with the President as the head and persons in charge of research, administration, finances, and facilities, University Vice Presidents and Division Directors with international responsibilities, and related institute directors participating. Necessary adjustments were made within the University to support design of the organization of this center.

At the establishment of this center, 5 persons from other institutes/faculties in the University assembled in this center as collaborative principal investigators, and thorough adjustment was made with those institutes/faculties in keeping with this center’s status as a priority target for the Organization for the Support and Development of Strategic Initiatives.

Specifically, adjustment and support were carried out so that there is no impediment to the research and education carried out by the institute/faculty in question; these support included securing replacement personnel and taking measures to reduce administrative and educational work loads.

(4) Its flexibility in applying, revising, or supplementing the host institution’s internal systems as needed for the center to effectively implement new management methods (e.g., English-language environment, merit-based pay, top-down decision making) unfettered by conventional modes of operation.

This center has been made an independent research organization reporting directly to the University President and kept separate from other research centers. University systems have been executed flexibly, making amendments and adjustments as necessary.

Specifically, English is the official language of the center, with the administrative tasks carried out in English and administrative documents made bilingual. Persons with high English proficiency were recruited from within and outside the University, and further training has been provided to some persons after entering the center as needed.

Under the management of the director, systems for determining salaries based on merit, for annual salaries, for evaluating researcher's achievements, for determining salaries based on evaluations of the work, and for renewal of contracts are being introduced.

Also, to deal with requests for flexible execution, improvement, or adjustment of systems in the center, the director exercises the functions established by the Organization for the Support and Development of Strategic Initiatives for dealing with research groups to take appropriate measures, subject to amendment through negotiation with the University President and related Vice Presidents and administrative divisions.

(5) Its accommodation of the center's infrastructural requirements (for facilities, e.g., laboratory space; equipment; land, etc

In order to assemble many leading researchers by making the center the one place where they want to work, the University used its Facility Department to the greatest extent to implement building of research facilities according to the plan that gives the center an outstanding research environment and distinctive tangible advantages so that it can claim with confidence to be a place for research of the highest level.

Specifically, construction of a new building to house the Center was completed successfully. The construction started in February 2014 and completed in May 2015.

The building has a total floor space of 8,000 square-meters and is designed as state-of-the-art research laboratories, incorporating opinions of researchers and the recent design trend of the world's leading research institutes. The building provides an optimum environment for creative studies to elucidate the fundamental mechanisms of sleep/wake. It is located close to Laboratory Animal Resource Center in the University, with which close collaboration is essential for the success of the Center. There is a natural pond named "Kasuga-ike" in front of the building, and the pond and its surround are arranged as a natural garden of the building. The modern research facilities surrounded by the natural atmosphere serve as the center of excellence for the studies of sleep/wake.

Until the construction had been completed, we continued to use the building that housed the FIRST Program, the Health and Medical Science Innovation Building, as main research facilities. However, its space available for the Center was limited, and it was provided with temporary floors on the Laboratory of Advanced Research and some labs in TARA Center in the University for rapid start-up of the studies.

Further, University of Tsukuba has provided university housing or satisfactory housing close to the University to researchers and administrative staff participating in this center, including foreign researchers. The University has also made its housing facilities available to foreign and Japanese researchers visiting this center so that they can hold seminars and carry out joint research.

(6) How it will support to sustain the center as a world premier international research center after the WPI-grant period ends.

As a concrete policy for raising the level of research to the highest international level, a goal proclaimed in the University's Midterm Plan, it is stated in this Plan that the University shall "promote high quality fundamental research taking a long term view of academic progress" and that "research groups and organizations which are expected to achieve outstanding research results will be singled out for appropriate support, including allocation of research resources, hiring of supporting personnel, and reforming of organizations, and will be aggressively promoted as international centers of research." The measures necessary to make this one of the world's leading centers, of which the University may be proud, shall be taken.

Specifically, in the third mid-term plan of University of Tsukuba starting from FY2016, it has set out a strategic framework of research resources over the entire university and planned to reallocate it, based on evaluation of research activities/achievements. Tenure positions are also subjected to the reallocation. The President, University of Tsukuba, Dr. Nagata has committed himself to offer a tenure position to the PI that produces sufficient research achievements in IIIS by using the planned reallocation system, so that IIIS will survive as a World premier international research center beyond the end of the WPI program implementation period. Details shall be decided upon consultation between the Vice Presidents in charge of Research and Personnel Affairs.

(7) Other types of assistance it will provide to give maximum support to the center in achieving its concepts and objectives and becoming a world premier international research center in both name and deed.

The University of Tsukuba is striving to be an “open university,” and is leading the way in realizing a flexible education and research organization and the new university organization demanded by tomorrow’s society. With this as the conceptual basis of our policies, we have introduced reforms in Japan’s universities. Dr. Sin-itiro Tomonaga, Dr. Leo Esaki, and Dr. Hideki Shirakawa are Nobel prize Laureates associated with the University, and in recent years, two of the centers of the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program) created by the Japanese government are being run in the University.

Also, in order to make the University more international, it is one of 13 universities promoting the formation of a network, Global 30, that makes international interactions a part of daily activities, and that makes the University into a world center of knowledge.

A University of Tsukuba research administrator (URA) headquarters (headquarters chief: the Vice President in Charge of Research) which is charged with carrying out business involving the URAs who are sent from the Ministry of Education, Culture, Sports, Science and Technology provide support for research strategies, international joint efforts, compliance with legal and social requirements, etc. that are key to this center’s research activities.

In order to truly raise the research level of this center as high as any in the world, the know-how and resources which can be the basis of such accomplishments must be exploited to the maximum extent. It is the responsibility of the University to see that this is carried out, by supplying all necessary support.

List of Principal Investigators

- If the number of principal investigators exceeds 10, add columns as appropriate.
- Place an asterisk(*) by the name of the investigators who are considered to be ranked among the world's top researchers.
- Give age as of 1 April 2017.
- For investigators who cannot participate in the center project from 1 April 2017, indicate the time that their participation will start in the "Notes" column.

Name		Age	Current affiliation (organization, department and specialties)	Academic degree	Notes
1	Masashi Yanagisawa*	56	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Neuroscience, Pharmacology	
2	Takeshi Sakurai*	52	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D., Neuroscience	
3	Hiromasa Funato*	47	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba Associate Professor, Univ Toho	M.D., Ph.D. Neuroscience	
4	Yoshihiro Urade*	63	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Biochemistry Neuroscience	
5	Robert Greene*	66	Professor, Department of Psychiatry, University of Texas Southwestern Medical Center, Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Neuroscience	
6	Qinghua Liu*	45	Associate Professor, Department of Biochemistry, University of Texas Southwestern Medical Center Professor, Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Genetics, Molecular Biology, Biochemistry	

(Appendix)

Name		Age	Current affiliation (organization, department and specialties)	Academic degree	Notes
7	Hiroshi Nagase*	69	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Medicinal Chemistry, Organic Chemistry	
8	Makoto Satoh*	61	International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Sleep Medicine	
9	Ichiyo Matsuzaki*	57	Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Occupational Psychiatric Medicine, Space Medicine	
10	Hitoshi Shimano*	57	Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Endocrinology, Metabolism	
11	Kumpei Tokuyama*	63	Professor, Faculty of Health and Sport Sciences, University of Tsukuba	Ph.D., Sports Medicine	
12	Akiyoshi Fukamizu*	57	Professor, Tsukuba Advanced Research Alliance, University of Tsukuba	Ph.D., Molecular Biology	
13	Satoru Takahashi*	55	Professor, Laboratory Animal Resource Center, Department of Anatomy and Embryology, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Developmental biology	
14	Joseph Takahashi*	65	Professor, Department of Neuroscience, University of Texas Southwestern Medical Center	Ph.D., Neuroscience	

(Appendix)

Name		Age	Current affiliation (organization, department and specialties)	Academic degree	Notes
15	Carla Green*	54	Professor, Department of Neuroscience, University of Texas Southwestern Medical Center	Ph.D. Molecular Biology, Biochemistry, Circadian rhythms	
16	Yang Dan*	49	Professor, Department of Molecular and Cell Biology, University of California, Berkeley, HHMI	Ph.D., Neurobiology	
17	Tetsuo Shimizu*	64	Professor, Department of Neuropsychiatry, Akita University Graduate School of Medicine	M.D., Ph.D., Psychiatry	
18	Hitoshi Okamura*	64	Professor, Graduate School of Pharmaceutical Sciences, Kyoto University Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Chronobiology	
19	Kaspar Vogt	50	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Physiology, Pharmacology, Neurobiology	
20	Michael Lazarus	47	Associate Professor International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Neuroscience	
21	Masanori Sakaguchi	40	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Brain regeneration and sleep	

(Appendix)

Name		Age	Current affiliation (organization, department and specialties)	Academic degree	Notes
22	Yu Hayashi	36	Associate professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Science	