

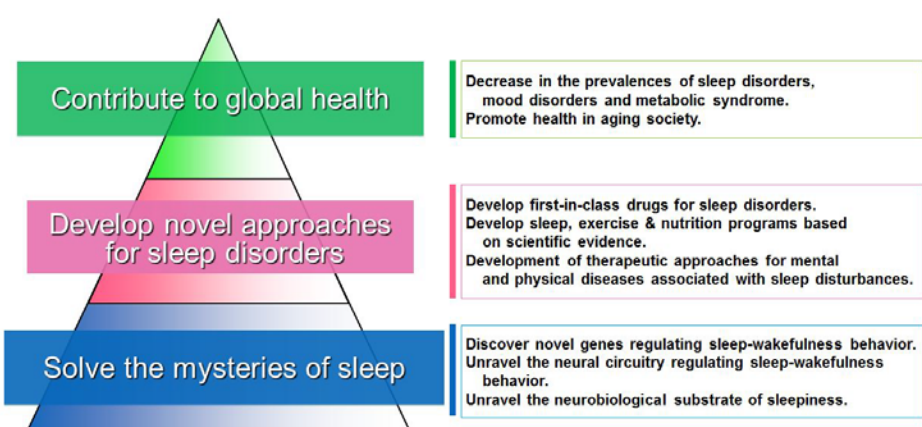
# Summary of Proposal

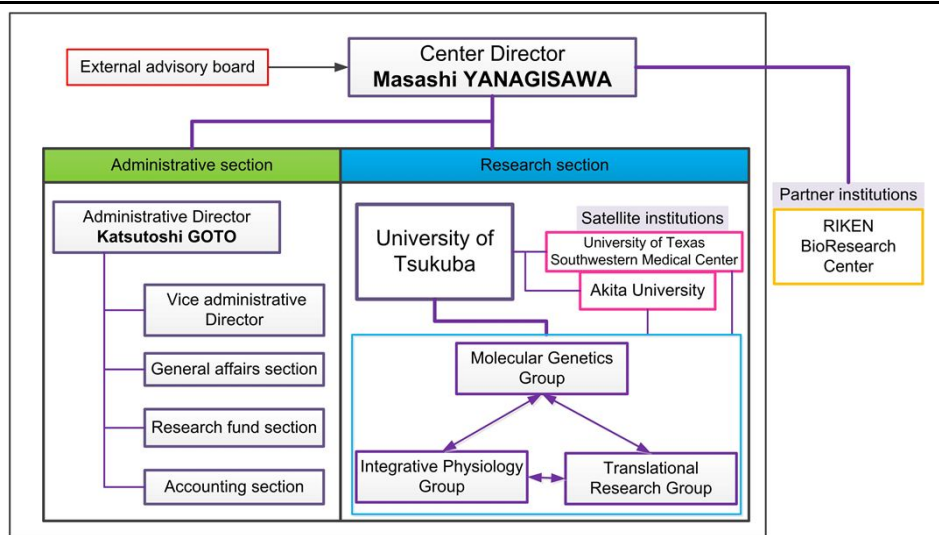
Host institution	University of Tsukuba
Chief entire-project officer (Head of host institution)	Nobuhiro Yamada, President
Chief center-project officer	Masashi Yanagisawa, Center for Behavioral Molecular Genetics, Professor and Director
Center director	Masashi Yanagisawa, Center for Behavioral Molecular Genetics, Professor and Director
Center name	International Institute for Integrative Sleep Medicine
Project Summary	<p>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 proposed research center will gather the world prominent scientists from multiple research fields contributing to the neurobiology of sleep. We will aim at elucidating the fundamental mechanism of sleep/wake regulation by combining the cutting-edge methodologies of neurobiology, molecular genetics and physiology. We will induce the fusion of medicine, chemistry, pharmacology and biology 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 will strive 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.</p>
Mission statement and/or Center identity	<p>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.</p>
Target research field	<p><b><u>Name of the target research field</u></b> Sleep biomedicine</p> <p>Sleep biomedicine, as defined here, is an inherently interdisciplinary field in terms of methodology, spanning molecular genetics, cellular biology, neurophysiology, neurochemistry, pharmaceutical sciences, medicinal chemistry, and clinical and social medicine. While focusing on sleep, the 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.</p> <p><b><u>Importance of the target research field</u></b></p> <p>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.</p> <p><b><u>Research trend of this field</u></b></p> <p>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, multiple pharmaceutical companies are currently focused on developing new classes of sleeping pills, indicating the consensus among the domestic and overseas pharmaceutical industries that this field is highly important for drug discovery.</p> <p><b><u>Reasons why the project fit for this call for proposals</u></b></p> <p>Japan has been producing a number of researchers who have made significant accomplishments in the field of sleep biomedicine. 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 has been selected as one of the Principal Investigators for the FIRST Program of the Cabinet Office of Japan, which has allowed him to intensively promote sleep research at his new Center hosted by the University of Tsukuba.</p>
Research objectives	<p>The research objectives that the proposed 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.</p>
Outline of management	<p>Establish a top-down administrative system headed by the Center Director by fully utilizing his long-term experience at an American university.</p> <p>Under the supervision of the Administrative Director who is thoroughly knowledgeable in both the research contents of the center and the administrative affairs of the national university corporation, the administrative staff will be composed of the Administrative Director, Assistant Administrative Director, and the following three sections. (General affairs section, Accounting section, Research fund section).</p>

	<p><b>Decision-making system</b> In order to facilitate efficient and flexible administration of the research center, the Center Director will have 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.</p> <p><b>Allocation of authority between the center director and host institution</b> 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.</p>												
Researchers and other center staffs, satellites, partner institutions	Principal Investigators: 15 (foreigners 5) (Achieved by October, 2013), Total Researchers: 115 (foreigners 35) (Achieved by March, 2015), Total Staff at Core-Center: 169 (Achieved by March, 2015), Main principal investigators: Masashi Yanagisawa, Hiromasa Funato, Takeshi Sakurai, Yoshihiro Urade, Robert Greene, Qinghua Liu, Hiroshi Nagase, Ichiyo Matsuzaki, Hitoshi Shimano, Junichi Hayashi, Akiyoshi Fukamizu, Satoru Takahashi, Tetsuo Shimizu, Carla Green, Joseph Takahashi, Satellite: University of Texas Southwestern Medical Center, Akita University, Collaboration: RIKEN BioResource Center												
Administrative director	Katsutoshi Goto, Professor Emeritus, University of Tsukuba												
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 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 will be used as an official language at the research center. (7) Adopt a system for evaluating research and merit-based compensation. (8) Provide appropriate equipment and facilities, office and animal center (space exceeding 5000m <sup>2</sup> ) as a top world-premier research center. (9) Hold international symposia once a year, and invited seminar series twice a month. And hold a retreat once a year for the development of students and young researchers, promotion of collaborative researches, and also an increased sense of a family-like unity of the Center. Provide workshops at overseas Satellites to increase the visibility of the research center overseas.												
Outline of indicators for evaluating a center's global standing	<p>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</p> <p>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 2668 and for the article describing narcolepsy episodes in orexin-deficient mice, the number of citations are 1660. 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 prospective Center Director, has attained domestic funding worth 1.8 billion yen (US\$22,500,000,) over five years as the Core Researcher of the FIRST project. In addition, he secured an average of US\$1,260,556 per year of competitive funding in the U.S. in the last 5 years.</p> <p>iii) Goals to be achieved through the project (at time of interim and final evaluations) (at time of interim) 1. The citation indices of our publications surpass those at other premier research centers for sleep biomedicine, such as the Stanford Center for Sleep Sciences and Medicine. 2. It would be too early to evaluate graduate students and post-doctoral fellows who are alumni of the research center. (at time of final evaluations) The citation indices of our publications surpass those at other premier research centers for sleep biomedicine, 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</p>												
Securing research funding	The total amount of competitive research funding raised by the prospective Principal Investigators in the past five years is \$44,316,704 averaging at \$8,863,341/year. The University of Tsukuba will be responsible for the labor costs for the scientists who are full-time Principal Investigators or researchers at the University before participating in this research center, and for the full-time University staffs who were appointed to the administrative division of this research center. The University will provide support for securing sufficient research space and for moving into new space, and will be partially responsible for providing research funding. By providing the funding, the University will support the installation of equipment and facilities, renovation of research laboratories, and the administrative management of the research center.												
Exploiting the results of previously-initiated center-building efforts	<p>Program name: Funding Program for World-Leading Innovative R&amp;D on Science and Technology (FIRST Program) Project title: Molecular Mechanism and Control of Complex Behavior Representative's name: Masashi Yanagisawa Funding period: 2010-2014</p> <p><b>The reason why we believe that this WPI based on our existing FIRST program will succeed</b> Our forward genetic screening of mutagenized mice for sleep/wake abnormalities, which is enabled by the FIRST program, has been going on smoothly with promising positive results. Our suite of cutting-edge equipment and experimental systems developed under the FIRST program constitute an ideal environment where the prospective top Principal Investigators of this WPI Center can productively explore their research ideas.</p> <p><b>Our prospects after the FIRST program</b> Use the Health and Medical Science Innovation Laboratory as the core facility of the Center.</p>												
Appropriations plan (Exchange Rate: JPY/USD=80)	FY	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total (\$ millions )	
	WPI grant	3,127	5,770	7,020	7,020	7,020	7,020	7,020	7,020	7,020	7,020	65,057	

	Funding for previously-initiated center-building efforts (if any)	1,008	1,730	1,730	1,730	1,730	1,730	1,730	1,730	1,730	1,730	16,578
	Total	4,135	7,500	8,750	8,750	8,750	8,750	8,750	8,750	8,750	8,750	81,635
Summary of host institution's commitment	<p><b><u>How positioned within the host institution's mid-to-long-term strategy plan</u></b>  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 will specify "International Institute for Integrative Sleep Medicine" for a Midterm Plan in the near future.</p> <p><b><u>Concrete Measures</u></b></p> <ol style="list-style-type: none"> <li>1) Provide at least the same level of resources as funded by this project.</li> <li>2) Enable top-down decisions by the Center Director regarding personnel affairs and budgets.</li> <li>3) Make necessary adjustments to assemble persons from other institutes of the University.</li> <li>4) Amend the regulations, if necessary, to accommodate the new system of management.</li> <li>5) Provide &gt;5,000m<sup>2</sup> of floor space that a "globally visible" premier research center deserves.</li> <li>6) Support to sustain the Center after this program ends.</li> </ol>											

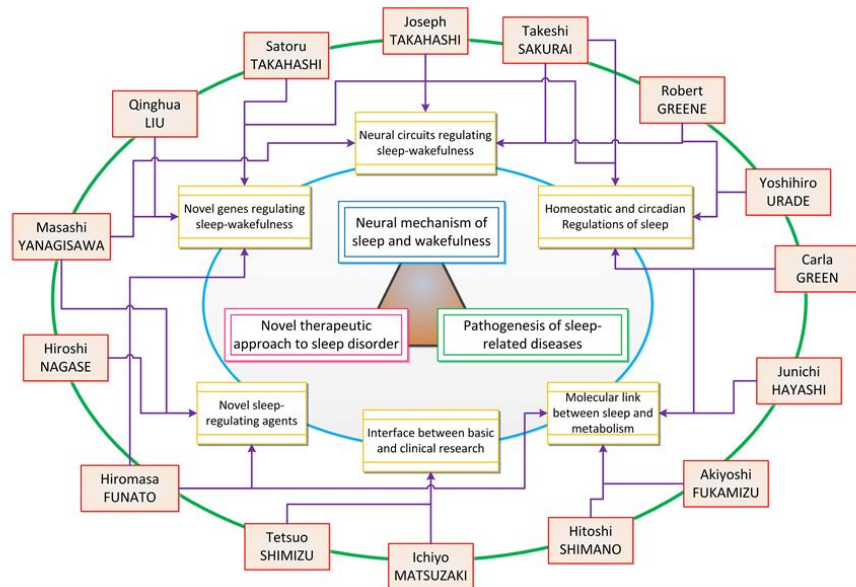
# Research Center Project

Host institution	University of Tsukuba						
Chief entire-project officer (Head of host institution)	Nobuhiro Yamada, President						
Chief center-project officer	Masashi Yanagisawa, Center for Behavioral Molecular Genetics, Professor and Director						
Center director	Masashi Yanagisawa, Center for Behavioral Molecular Genetics, Professor and Director						
Center name	International Institute for Integrative Sleep Medicine						
Project summary	<p>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 proposed research center will gather the world prominent scientists from multiple research fields contributing to the neurobiology of sleep. They will 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.</p> <p><b><u>The general plan of the project</u></b></p> <p>At the proposed Center, we will aim at elucidating the fundamental mechanism of sleep/wake regulation by combining the cutting-edge methodologies of neurobiology, molecular genetics and physiology. We will induce the fusion of medicine, chemistry, pharmacology and biology 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 will strive 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.</p>  <table border="1" data-bbox="494 1232 1420 1657"> <tr> <td>Contribute to global health</td> <td>Decrease in the prevalences of sleep disorders, mood disorders and metabolic syndrome. Promote health in aging society.</td> </tr> <tr> <td>Develop novel approaches for sleep disorders</td> <td>Develop first-in-class drugs for sleep disorders. Develop sleep, exercise &amp; nutrition programs based on scientific evidence. Development of therapeutic approaches for mental and physical diseases associated with sleep disturbances.</td> </tr> <tr> <td>Solve the mysteries of sleep</td> <td>Discover novel genes regulating sleep-wakefulness behavior. Unravel the neural circuitry regulating sleep-wakefulness behavior. Unravel the neurobiological substrate of sleepiness.</td> </tr> </table> <p><b><u>The Center's overall structure</u></b></p> <p>The proposed administrative structure will provide the Center Director with sufficient authority to enable a timely and flexible decision-making. The University of Tsukuba will host the Core site, while the Satellites will be located at the University of Texas Southwestern Medical Center and the Akita University. Although several research "groups" are depicted, the Center will constantly encourage 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.</p>	Contribute to global health	Decrease in the prevalences of sleep disorders, mood disorders and metabolic syndrome. Promote health in aging society.	Develop novel approaches for sleep disorders	Develop first-in-class drugs for sleep disorders. Develop sleep, exercise & nutrition programs based on scientific evidence. Development of therapeutic approaches for mental and physical diseases associated with sleep disturbances.	Solve the mysteries of sleep	Discover novel genes regulating sleep-wakefulness behavior. Unravel the neural circuitry regulating sleep-wakefulness behavior. Unravel the neurobiological substrate of sleepiness.
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Solve the mysteries of sleep	Discover novel genes regulating sleep-wakefulness behavior. Unravel the neural circuitry regulating sleep-wakefulness behavior. Unravel the neurobiological substrate of sleepiness.						



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

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



Mission statement and/or Center 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.

(1) Target research field

**Name of the target research field**

Sleep biomedicine

Sleep biomedicine, as defined here, is an inherently interdisciplinary field in terms of methodology, spanning molecular genetics, cellular biology, neurophysiology, neurochemistry, pharmaceutical sciences, medicinal chemistry, and clinical and social medicine. While focusing on sleep, the 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, multiple pharmaceutical companies are currently focused on developing new classes of sleeping pills (including those targeting the orexin pathway), indicating the consensus among the domestic and overseas 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 is the foundation of the present proposal, is the only multi-investigator research center in Japan that is specifically focusing on sleep biomedicine. This has been 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.

### **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 biomedicine. 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 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 has been selected as one of the Principal Investigators for the FIRST Program (2009-2013) of the Cabinet Office of Japan, which has 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 biomedicine. Moreover, the present WPI-Focus, if funded, will allow 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 has been conducting his research for over 20 years. His presence will further elevate the level of Japan's expertise in sleep biomedicine.

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 proposed center has an international appeal to it not only because of the Japanese researchers gathered at the Center but also the participation of the several prominent U.S. 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 will make the Center further internationally appealing, which will attract 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 will be a great help. Yanagisawa has been based at an American university for over 20 years while sustaining his mental identity as Japanese; his experiences (both as an U.S.-based researcher returning back to Japan, and as a person who has lived in America as a "foreign immigrant") will allow him to manage the proposed 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 will aim to become an international hub of sleep biomedicine 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 biomedicine 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 biomedicine 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 biomedicine in the near future. This proposed 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 is the basis of the present center proposal, we are fully operating 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 have already produced and will continue to produce numerous mouse lines for cell type-specific and time-dependent control of multiple genes of interest, including the orexin related genes. Thus, we have established a core of the cutting-edge research environment; the present proposal will allow us to expand and improve this core environment into a globally visible, long-term sustainable hub of multi-investigator cooperation.

In order to make the proposed center into a truly interdisciplinary site for the "fusion of research fields," the following researchers will participate: 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; Junichi Hayashi, who is the first in the world to succeed in producing a mouse strain termed the "mito-mouse", a mouse harboring pathogenic mutations in the mitochondrial genome; 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 will facilitate the integration of research themes interfacing sleep/wake regulation, cellular and organismal 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 proposed 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 are participating in the Center use genetically engineered mice as their routine resource, Satoru Takahashi will also actively participate, who is the Director of the Laboratory Animal Resource Center at the University of Tsukuba. His core-facility support will be essential, including the generation, transportation and management of transgenic mice.

Thus, the proposed center, while having its sharp focus on sleep biomedicine, will have 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 will allow the Center to sustain a world-class level of research in the target field for long term.

## (2) Research objectives

The research objectives that the proposed 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. Over all, our current level of understanding is rudimentary at best. We will conduct precise neurophysiological analyses of these known components. We will dissect neuronal and molecular mechanisms of sleep regulation by circadian clocks and sleep-inducing substances. At the same time, we will 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]

- **Forward genetic approach to identify new key genes involved in sleep/wake regulation (Yanagisawa, Funato, Takahashi, J)**

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 has now been expanded as one of the major pillars of the FIRST Project at the University of Tsukuba, where we also



collaborate with Shigeharu Wakana at RIKEN BioResource Center in Tsukuba (Partner Institution in this proposal). The large-scale screening at Tsukuba has been carried out smoothly with a sustained throughput of 60-80 mice screened per week. We have so far screened ~4,000 mice by EEG/EMG-based true sleep analysis, and detected at least 4 pedigrees of mice exhibiting marked, heritable abnormalities in sleep/wake. At present, the project is in the stage of identifying the causative gene by SNP-based linkage mapping and whole-exome sequencing, while continuing the primary screen. The heritable sleep abnormalities so far confirmed include: substantially increased wakeful time, substantially increased non-REM sleep time, and markedly abnormal REM sleep architecture. We believe that these strong phenotypes are caused by mutations in the genes that function within the core machinery of sleep/wake regulation. We will directly close in on the regulatory mechanism of sleep/wake by discovering new sleep/wake-regulating genes from these mutant mice.

- **Optogenetic and pharmacogenetic approach to understand the mechanistic principles of neural circuitry for sleep/wake regulation (Yanagisawa, Sakurai, 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 proposed research center, he will jump in to the field of sleep neurobiology and examine the regulation of sleep/wake by brain micro-RNAs, of which the function in the CNS largely remains a mystery. By combining these various methods, we will clarify the principles of neural circuit operation that controls sleep/wake behaviors.

- **Elucidation of the mechanisms of action of sleep substances (Urade and Greene)**

Urade has investigated the mechanism for the sleep-inducing action of prostaglandin D2 and discovered that it was 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, will be further investigated and how it relates to the homeostatic mechanism of the sleep/wake will be examined.

- **Elucidation of molecular mechanism of circadian rhythm and impacts of its disruption on sleep (Takahashi and Green)**

The identification of the Clock gene by Takahashi triggered an explosive advancement in the understanding of circadian clock mechanisms. Recently, it has become increasingly clear that disruption of clock genes can trigger dysregulation of insulin secretion and other metabolic abnormalities, suggesting a strong link between disruptions of circadian rhythm and aspects of metabolic syndrome. Takahashi will continue these lines of investigation, linking the sleep abnormalities, circadian rhythm disruptions, and metabolic dysregulation. Green studies molecular mechanisms that link the circadian rhythm to metabolic syndrome through the research on the circadian-regulated mRNA 3'-adenylase nocturnin. At the UTSW Satellite of this research center, they will study how the circadian rhythm and sleep are related and the multifaceted impacts of disrupted circadian rhythm on individuals. Takahashi will also continue to provide his expertise in gene identification in mutagenized mice (see above).

## **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 peripheral organ-brain interactions in the regulation of sleep/wake behavior.**
- **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 will be studied.

[Approaches necessary to accomplish research objectives]

- **Physiological and endocrinological research on the association of abnormal metabolism and sleep/wake disruption (Shimano, Funato, Takahashi)**

Shimano has been making significant contributions for the elucidation of intracellular signaling and transcriptional control related to lipid/cholesterol metabolism. Recently, he has generated mice that have an abnormal lipid composition in the brain by disrupting the gene for a lipid modification enzyme. The effects of the lipid composition on the brain function are mostly still unknown. Studies will be conducted to determine the behavioral consequences of the abnormal brain lipid composition and metabolism, including sleep/wake abnormalities. Funato has elucidated the complex regulation of feeding behavior and body weight by orexin neurons. He will continue to dissect the neural circuits for orexin that are involved in sleep/wake, energy homeostasis, and glucose metabolism. By combining retrograde trans-synaptic viral vectors and transgenic carrier mice, the cross talk between the brain and the peripheral organs in the energy metabolism will be investigated.

- **Investigation on the link between sleep/wake disruptions, metabolic dysregulation, and cellular metabolism/respiration and signaling (Hayashi and Fukamizu)**

Hayashi is a globally recognized expert in the cell biology and genetics of mitochondria, the intracellular generators of energy. At the proposed center, his laboratory will focus on the bilateral relationship between the mitochondrial and cellular energy metabolism and sleep/wake at the organismal level. Hayashi has succeeded in producing mice carrying the pathogenic mutant mtDNA, and by using these mice, effects of mitochondrial dysfunction on sleep/wake behavior will be examined. Reciprocally, the mitochondrial functions will be studied in sleep-deprived mice and in transgenic mice showing sleep/wake abnormalities. Fukamizu will study how the sleep/wake cycle and energy/glucose metabolism are related by using various transgenic mice with altered FOXO transcription factors and other intracellular signaling pathways. We will aim at linking the metabolic/respiration pathways at the cellular level to the changes occurring at the organismal level such as sleep/wake and systemic energy homeostasis.

### **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 “good sleep” program, a multidimensional non-drug intervention, to prevent sleep-related disorders based on the evidence of basic and clinical studies.**

We will develop new drug-candidate compounds modulating sleep/wake that are different from existing sleep-inducing agents or psychostimulants in their mechanism of action. We will 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 will utilize such associations in order to elucidate the molecular mechanisms behind the association.

[Approaches necessary to accomplish research objectives]

- **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, has gone through a large Phase III clinical trial as a sleep-inducing drug, producing highly promising results. 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 have carried out a high-throughput screening of a library of ~250,000 drug-like compounds at UTSW and identified several distinct chemical classes of orexin receptor agonists. Based on information obtained by this screening, we will embark upon a serious medicinal chemistry efforts in order to further improve compounds' potency, blood-brain-barrier permeability, and oral bioavailability. We fully realize that making a CNS-available agonist for peptidergic receptor is a formidable challenge in medicinal chemistry. Nagase's experience of creating two first-in-class marketed drugs will be fully utilized here. Candidate agonists will be subjected to various cell-based, ex vivo and in vivo assays, not only in order to test them as drug candidates but also to use them as pharmacological tools for further dissecting the orexin biology.

- **Identification of novel sleep/wake modulating substances and their mechanism of action by in vivo screen of compound libraries (Funato, Yanagisawa, Nagase)**

In addition to the above-described target-based approach of drug discovery, we will attempt a "black-box" in vivo screen of small-scale compound libraries in order to identify novel sleep/wake modulators. As mentioned above, because of the ongoing forward genetic screening for sleep/wake mutant mice, we already have a large-scale system for mouse sleep recording fully up and running. We will utilize this facility to screen a pre-selected subset of 1,000-2,000 drug-like compounds in vivo, by administering a mixture of ~10 compounds per mouse (multiplexing) while EEG sleep-recording them. If a novel (or unexpected) sleep/wake modulating compound is found, we will decipher its molecular target and mechanism of action, and initiate medicinal chemistry efforts to improve the initial hit. This will hopefully lead not only to the discovery of a new sleep-regulatory pathway but also to a novel drug candidate.

- **Development of new assessment and preventive measures for sleep disorder patients and high risk groups (Shimizu and Matsuzaki)**

Workers in modern societies are constantly deprived of sleep and immersed in environments where they can develop full-blown sleep disorders and mood disorders. It is important to identify a high-risk group for developing sleep disorders at an early stage, and perform the appropriate intervention. At the proposed research center, we will try to remedy sleep disorders not only by using drug treatments but also by providing lifestyle guidelines for getting a healthy sleep, nutrition, and exercise. We will also develop appropriate assessments and measures in order to prevent high-risk groups from developing serious diseases. Shimizu has been single-handedly undertaking a majority of orexin peptide measurements in Japanese patients, and established a network between patients and medical institutions concerning sleep disorders and related conditions. Matsuzaki, as a leader of the industrial psychiatry field, has an established network in the client industries. Such networks allow us to verify the accuracies of assessments and efficacies of intervention. Matsuzaki and Shimizu function as an interface between the clinical environment and research laboratories, e.g., by translating knowledge gained from mouse models to patients, and conversely, by providing laboratory-testable hypotheses derived from the findings in patients. Networks Shimizu and Matsuzaki have generated will increase the visibility of this research center, and will also be tremendously helpful in the future clinical trials of the sleep disorder drug being developed by Nagase and Yanagisawa. In addition, Matsuzaki also specializes in the field of aerospace psychiatry and is a member of the Japan Aerospace Exploration Agency (JAXA), which conducts studies on sleep and psychological stress under microgravity by using astronauts as unique research subjects.

### (3) Management

#### i) Center director

Masashi Yanagisawa (52 years old), Center for Behavioral Molecular Genetics, Professor and Director.

Specialties: Neuroscience, Pharmacology.

Professor Yanagisawa is one of few scientists who made two outstanding discoveries of bioactive peptides. Both discoveries revolutionized the research field and have brought clinical benefits.

In 1988, when he was a graduate student, he and his colleagues identified “endothelin” as a potent vasoconstrictor factor produced by endothelial cells. Subsequently, he and his colleagues at the University of Tsukuba succeeded in cloning endothelin receptors. He was highly recognized for the discovery of endothelins and their receptors so that when he was 31 years old, he was recruited by Joe Goldstein and Mike Brown to the University of Texas Southwestern Medical Center, and started his own lab as an associate professor and associate investigator of the Howard Hughes Medical Institute. As a PI, he succeeded in cloning of endothelin converting enzymes. During the course of his research on gene targeted mice, he and his colleagues have unexpectedly demonstrated that the endothelin pathways are important in the embryonic development of neural crest-derived tissues, and have led to the discovery that endothelin and endothelin receptor mutations cause Hirschsprung’s disease and related neurocristopathies in humans. In adult pathophysiology, endothelin is implicated in various conditions involving abnormal vascular tone and remodeling, and endothelin receptor antagonists are in clinical use as a mainline drug for the treatment of pulmonary hypertension since 2001.

Around 1995-1996, he started a risky endeavor of finding novel bioactive molecules by “de-orphanizing” orphan G protein-coupled receptors. In 1998, his group published the discovery of “orexins,” endogenous neuropeptide ligands for two orphan G protein-coupled receptors. Orexin is expressed exclusively in the lateral hypothalamic area, which was considered a “feeding center.” In the following year, his laboratory unexpectedly discovered that orexin-deficient mice suffered from narcolepsy, a sleep disorder characterized by excessive daytime sleepiness and abnormal intrusion of REM-sleep phenomena. Subsequent results from his laboratory indicate that supplying exogenous orexin peptides, either transgenically or pharmacologically, completely rescues narcoleptic mice that lack endogenous orexin neurons. Since it has been shown that the vast majority of human narcoleptic patients are orexin-deficient, Yanagisawa’s studies open up the possibility of replacement therapy of the disease using orexin receptor agonists. The orexins have turned out to be a major key to understanding wakefulness, motor control during sleep, and motivation and addiction during wakefulness. Recently, he and his colleagues showed the critical role of orexin receptor type 2 in regulating body weight, which drives the current drug discovery project for anti-obesity drug. For his outstanding achievements, he was elected to a member of the U.S. National Academy of Sciences in 2003.

Because he has run his own lab in the U.S. for more than 20 years, he is familiar with the strengths and limitations of both the research and administrative systems of top U.S. research universities. He also conducted his own lab in Japan by the research funding program, Exploratory Research for Advanced Technology (ERATO), and now running his own lab at the University of Tsukuba by Funding for World-Leading Innovative R&D on Science and Technology (FIRST). Thus, he is the right person to bring merits and strengths of the U.S. academic system to Japan. He has a personal network of prominent researchers around the world, which makes him the most appropriate person as the Center Director to build a research center functioning as the “hub for research excellence.”

Currently, Professor Yanagisawa spends approximately half the year working in Japan to run his lab at the University of Tsukuba. If the present WPI application is funded, he intends to retire from the Howard Hughes Medical Institute and will be fully committed to the full-time position as the Center Director.

ii) Administrative director

Katsutoshi Goto (69 years old), Professor Emeritus, University of Tsukuba

Professor Goto served as a professor of the Department of Pharmacology, Institute of Basic Medical Sciences, University of Tsukuba from 1990 to 2006, engaging himself in intensive research and education. He has profound understanding of the research objectives and methodologies of the prospective research center. He has plentiful exchange experiences with overseas researchers and is excellent at communicating in English.

When he was an associate professor at the Department of Pharmacology, he was involved in the research study that led to the discovery of endothelin, which allowed him to build a long and trusting relationship with the prospective Center Director, Masashi Yanagisawa.

He served as the Director of the Institute of Basic Medical Sciences, University of Tsukuba and also as the Director of Center for Tsukuba Advanced Research Alliance (TARA Center). He has abundant experiences with administrative affairs related to the conduct of research. He has a broad range of human connections in the University of Tsukuba because of his history. As described, he is the most appropriate personnel as the prospective Administrative Director of the research center from the viewpoints of his understanding for research, proficiency in language, relationship with the prospective Center Director, and relationship with the host institute.

### iii) Administrative staff composition

We will establish a strong supportive organization in order to decrease the burden of administrative obligations of scientists so that they concentrate on their research. In order to enable prompt decision-making and resolute implementation, increase the independence and autonomy of the proposed research center and establish 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 will put persistent efforts to reassess the research and administrative organizations. In addition, by assigning several full-time members of the University administrative staff to the research center, we will make 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 both the research contents of the center and the administrative affairs of the national university corporation, the administrative staff will be composed of the administrative director, assistant administrative director, and the following three sections.

- General affairs section (5 staff members)

General affairs section will be engaged in legal affairs, general affairs, personnel affairs, employment, travel, work management, public relations (outreach activities), symposia, conferences, and international affairs. One full-time University staff member who has a thorough knowledge of general affairs will be assigned to the Center. With regard to the support for a large number of foreign researchers coming to the Center, we will 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.

- Accounting section (4 staff members)

Accounting section will be 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 will be assigned to the Center.

- Research fund section (3 staff members)

The research fund section will be in charge of a wide variety of tasks related to competitive research funds, including information collection, application support, administrative affairs, and support for report preparations. One full-time University staff who is highly experienced in the affairs for securing research funds and knowledgeable of the governmental systems will be assigned to the Center.

#### 2. Use of English as the official language

English will be used as an official language at the research center. All assigned staff members will be fluent in spoken and written English, except for the people who have specific skills that cannot be replaced by any other people. Documentation will be 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 will preferentially hire people with overseas experiences and/or with an excellent command in

English language. The TOEIC/TOEFL scores and particularly the writing and speaking abilities will be considered as important factors for hiring. English language training sessions will be conducted regularly for the staff members. Once every two years, overseas training sessions will be recommended even to administrative staff members, providing them the opportunities to see the “cultural melting pot” and directly learn from the open-minded attitudes welcoming foreigners. Their experiences from such sessions will be used for creating a positive environment for foreign researchers at the Center.

iv) Decision-making system

In order to facilitate efficient and flexible administration of the research center, the Center Director will have 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 will be established to provide the Center Director with advice on the Center management by using video conference. In order to facilitate center-wide discussions of administrative matters and personnel recruitment, the Center Director can create and convene, as needed, various internal committees comprised of the Administrative Director and Principal Investigators.

The Administrative Director will supervise the administrative division and provide an environment where researchers can focus on their research. The Principal Investigators 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 host institution

By positioning the prospective 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 will be 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 Principal Investigators 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 U.S., which will make the most of the Center Director’s research and administrative experiences in the U.S. Moreover, the Center will establish and maintain 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 will earnestly consider 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 2012	Final goal (Date: month, year) (October, 2013)
		Those in existing center-building project		
Researchers from within the host institution	7	0	7	7
Foreign researchers invited from abroad	0	0	2	4
Researchers invited from other Japanese institutions	0	0	2	4
Total principal investigators	7	0	11	15

(At beginning)

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

(At end of FY2012)

The Center will have invited Takeshi Sakurai (currently at University of Kanazawa) to the Tsukuba Core as a Principal Investigator. The proposed Satellites will have been installed at the University of Texas Southwestern Medical Center and at the Akita University. Joseph Takahashi, Carla Green (Texas), and Tetsuo Shimizu (Akita), will join as Principal Investigators at the Satellites.

(Final goal (circa October, 2013))

All of the 15 proposed Principal Investigators will have joined the Center by FY 2013. Yoshihiro Urade (currently at Osaka Bioscience Institute), Hiroshi Nagase (Kitasato University), Robert Greene (UTSW), and Qunghua Liu (UTSW) will have been moved to the Tsukuba Core as Principal Investigators. Especially, the Center will provide generous startup funds to the two Principal Investigators recruited from abroad.

b) Total members

	Numbers			
	At beginning		At end of FY 2012	Final goal (Date: month, year) (March, 2015)
		Those in existing center-building project		
Researchers	41 < 1, 2%> [ 8, 20%]	7 < 0, 0%> [ 5, 71 %]	59 < 18 , 31%> [ 9, 15%]	115 < 35, 30%> [ 35, 30%]
Principal investigators	7 < 1, 14%> [ 0, 0%]	0 < 0 , 0%> [ 0, 0%]]	11 < 3, 27%> [ 1, 9%]	15 < 5 , 33%> [ 1, 7 %]
Other researchers	34 < 0 ,0 %> [ 8, 24 %]	7 < 0, 0%> [ 5, 71%]]	48 < 15, 31%> [ 8, 17%]	100 < 30, 30%> [ 34, 34 %]
Research support staffs	17	7	19	40
Administrative staffs	14	4	14	14
Total number of people who form the "core" of the research center	72	18	92	169

(At beginning)

The Center will be started with the 7 Principal Investigators from the University of Tsukuba and

the members in their respective laboratories. Eighteen members will join from the FIRST program.

(At end of FY2012)

The members of the Sakurai laboratory will have joined the Tsukuba Core.

(Final goal (March, 2015))

All of the 15 proposed Principal Investigators will have joined the Center by FY 2013. The members of the Urade and Nagase laboratories will have joined the Tsukuba Core. Two researchers will have been recruited to the laboratories of Takahashi and Greene at the Texas Satellite. We will employ all post-doctoral fellows through international solicitations; highly talented young scientists will be recruited over the years. The Center will have approximately 150 researchers overall by the end of FY2015.

ii) Collaboration with other institutions

[Satellite institutions]

1) University of Texas Southwestern Medical Center

A Satellite site will be installed at the University of Texas Southwestern Medical Center where the prospective Center Director Masashi Yanagisawa has been conducting his research for over 20 years. As Satellite Principal Investigators, two world-leading researchers in the field of circadian rhythm, Joseph Takahashi and Carla Green, will participate. A total of two WPI-funded post-doctoral fellows will be hired for these laboratories. A close collaboration with the Takahashi laboratory has been ongoing for over two years already, concerning the mouse forward genetics project. His continued contributions will be essential in order to carry through the project. The presence of Takahashi and Green will further elevate the global visibility of this WPI Center.

2) Akita University

We will establish 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.

In order to facilitate the progress of research based on intimate interactions between the Tsukuba Core and the Satellite sites, we will have internet-based weekly 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

Shigeharu Wakana of the Technology and Development Team for Mouse Phenotype Analysis, RIKEN BioResource Center, has identified a large number of pathogenic mutations from their systematic ENU-mutagenesis screening in mice. He is also a Japan representative of the International Mouse Phenotyping Consortium (IMPC). We have an ongoing close collaboration with his team in our forward genetic screening and mapping of sleep/wake mutant mice, which is a major pillar of the FIRST project. RIKEN BioResource Center will serve as a partner institution in the present proposal, and function as the local provider of ENU-mutagenized mice, and as the core facility for systematic mouse phenotyping.

(5) Research Environment

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

1. Support by administrative division

We will implement an administrative support system that will reduce the burden of administrative obligations of researchers and allow them to devote themselves exclusively to their research. Our



administrative team will 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 national universities, the administrative division will function autonomously and independently from the University administration. Specifically, the administrative division will fully and promptly perform any necessary support for the conduct of research, including legal affairs, general affairs, personnel affairs, employment, travel, work management, public relations (outreach activities), symposia, conferences, international affairs, 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, administrative affairs, and support for report preparations.

## 2. Exempting on-campus researchers from non-research institutional duties, while providing support for their affiliated departments

Regarding those top researchers who are recruited to and participate in the Center from within the University of Tsukuba, the Center will ensure that they can further their research without hindrance, by cooperating with their affiliated departments. Those researchers will be exempted from some of their non-research duties at their affiliated departments. In return, we will compensate their affiliated departments by providing relevant personnel costs.

## 3. 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). The town of Tsukuba has an advantage of being built an international research park. The Japan International Science and Technology Exchange Center (JISTEC) is located in Tsukuba and provides a wide range of living support for researchers from foreign countries. Partly in collaboration with JISTEC, the Center will provide various supports, including visa application, paperwork such as alien registration, opening bank account, purchasing insurance, and arranging for residence. The University of Tsukuba will offer the university guesthouses and its affiliated housings nearby for the researchers (especially foreigners) and administrative staff members who are recruited to work in this research center. For the researchers who visit the Center to attend seminars or to conduct collaborative research, various accommodation facilities of the University will be available.

- 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 are recruited to the Tsukuba Core from other institutions (especially those from overseas institutions), the Center will provide a sufficient amount of startup research funding. The amount of the startup fund will be individually considered and negotiated, but will be similar to startup funds in the U.S. academia under equivalent situations. It will be decided by the Center Director who has plentiful experience in the U.S. academia. When it is time for them to apply for external funding, the administrative division will provide strong administrative support 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 will be 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), 8. Personal international networks of the Center Director and Principal Investigators.

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 will be aggressively promoting the participation of outstanding post-doctoral fellows, especially foreign researchers and

female scientists.

The Center Director will strive 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 will strive to achieve research accomplishments sufficiently high so that they will then be recruited by other institutions for the next career stage. This will 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 will be conducted in English at the Center. In addition, all administrative staff members will be fluent in spoken and written English, except for the people who have specific skills that cannot be replaced by any other people. Documentation will be 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 will be considered as important factors when appointing administrative personnel. English language training sessions will be conducted regularly for the staff members. Once every two years, overseas training sessions will be recommended even to administrative 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)

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

The Principal Investigators and other independent researchers will be annually evaluated by the external advisory board, considering publications and their citations, invitations to international meetings, level of external funding, generation of significant intellectual properties, etc. 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.

When inviting Principal Investigators and other independent investigators from outside of the host institution, their salaries will be 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 will be 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 will 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, the Center will be provided with all floors on the E Building of the University of Tsukuba Hospital, which will be vacated by January, 2013 into the new ward building currently under construction. The Center will continue to use the floors on the Health and Medical Science Innovation Laboratory that are currently occupied by the FIRST Program. Together, the Center will be provided with more than 5,000 m<sup>2</sup> of research floor space. The Hospital E Building is located in close physical proximities to both the Innovation Laboratory and the Laboratory Animal Resource Center, which should be highly advantageous. During the required renovation of the E Building, the Center will be provided with temporary floors on the Laboratory of Advanced Research D.

The building that houses the current FIRST Program, the Health and Medical Science Innovation Building, was newly constructed in 2011, incorporating the recent design trend of overseas research laboratories. It has a coffee-break area on each floor, which can be a place for casual communications between researchers. On the top floor is a large, 200-people conference room. The Center's own seminar series will be held there, providing opportunities for exchanges among the Center members and with other researchers on campus.

Regular intra-laboratory and Inter-laboratory research meetings will be held by using internet-based video conferencing services (such as Skype), so that the meeting is attended by the Principal Investigators and researchers at the Satellite sites. The prospective Center Director has been managing his two laboratories across the Pacific (Tsukuba, Japan and Dallas, Texas) for over two years now. These spaces for communication will continue to function as the key facility of the WPI center after its establishment.

The existing research facility for the FIRST program is equipped with shared capital devices such as a system for large-scale mouse EEG/EMG recording and analysis, a fiber-optic fluorescence confocal endo-microscope, a two-photon microscope with electrophysiology rigs, multiple sets of slice and cellular patch-clamp station, and an ultra-low-power, wide-field confocal microscope. Cutting-edge shared devices will be systematically acquired in the proposed center, according to the requirements of its laboratories.

Additional capital equipment will be available to the Center through the Open Facility function of the University, which is scheduled to start sometime this fiscal year. This includes such equipment as cutting-edge mass spectroscopy, super-high resolution ultrasound echo sonography for mice, and in vivo luminescence/fluorescence imaging system for mice. This function will be expanded in stages, and will make possible the use of the pioneering research facilities in the Tsukuba area.

- 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 prospective Center Director served as the organizer of the international symposium "Frontiers in Behavioral Brain Science ~ Solving the Mystery of Sleep" through the 2011 Funding Program for World-Leading Innovative R&D on Science and Technology (open seminars of the FIRST program). We could gather a total of 16 prominent researchers in the field as invited speakers, including a Nobel Laureate (9 from the U.S., 3 from Europe, and 4 from Japan). The symposium was conducted in English including all oral and poster presentations.

In order to create a "globally visible research center", we will regularly hold similar symposia once a year, and invited seminar series twice a month. Moreover, we will hold a retreat once a year for the development of students and young researchers, promotion of collaborative researches, and also an increased sense of a family-like unity of the Center. Providing workshops at overseas Satellites will also increase the visibility of the research center overseas.

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

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, will provide the Center with additional know-how on development strategies, international cooperation, and compliance.

Graduate students conducting thesis studies at the Center will be, as a rule, all hired as research assistants (RA). Based on the objectives of the 3<sup>rd</sup> and 4<sup>th</sup> Science and Technology Basic Plans, the level of their salaries will be the amount equivalent to living expenses. By providing reasonable compensations, the graduate students will concentrate on their research activities as their professional work. The prospective Center Director discovered endothelin when he was a graduate student. In that spirit, the Center will promote creative researches through casual but intensive discussions with young graduate students who have flexible and free ideas.

(6) 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  
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 U.S., 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 prospective Center Director's work, the number of citations for the article that reported the discovery of orexins is 2668 and for the article describing narcolepsy episodes in orexin-deficient mice, the number of citations are 1660. These high numbers of citations suggest that these articles are remarkable reports that greatly affected research activities of other researchers in the field.
2. The existing FIRST research core is so new and this way of evaluation is impossible at this point. However, speaking of the research laboratory of the prospective Center Director, Masashi Yanagisawa, many researchers who received trainings 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 will attract excellent graduate students and post-doctoral fellows to this research center.
3. Masashi Yanagisawa, the prospective Center Director, has attained domestic funding worth 1.8 billion yen (US\$22,500,000,) over five years as the Core Researcher of the FIRST project. In addition, he secured an average of US\$1,260,556 per year of competitive funding in the U.S. in the last 5 years.

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

(at time of interim)

1. The citation indices of our publications surpass those at other premier research centers for sleep biomedicine, such as the Stanford Center for Sleep Sciences and Medicine.
2. It would be too early to evaluate graduate students and post-doctoral fellows who are alumni of the research center. However, some of them would have started to move their way up to the next stage of various career paths, including those at overseas research facilities.
3. Maintain the current level of research grant acquisition.

(at time of final evaluations)

1. The citation indices of our publications surpass those at other premier research centers for sleep biomedicine, 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 current level of research grant acquisition.

(7) Securing research funding

i) Past record

2007: \$8,193,448

2008: \$7,244,905

2009: \$6,646,950

2010: \$10,990,915

2011: \$11,240,486

(Exchange rate for 1 U.S. Dollar = 80 yen)

The total amount of competitive research funding raised by the prospective Principal Investigators in the past five years is \$44,316,704 averaging at \$8,863,341/year.

ii) Prospects after establishment of the center

The University of Tsukuba will be responsible for the labor costs for the scientists who are full-time Principal Investigators or researchers at the University before participating in this research center, and for the full-time University staffs who were appointed to the administrative division of this research center. The University will provide support for securing sufficient research space and for moving into new space, and will be partially responsible for providing research funding. By providing the funding, the University will support the installation of equipment and facilities, renovation of research laboratories, and the administrative management of the research center.

At the time of this application, competitive research funds for 2012 and 2013 have already been secured through the FIRST program. Applications for other large-scale research grants are in progress. Considering the level of competitive research funds acquired by the prospective Principal Investigators in the recent past, we expect that we will be able to secure about the same level of research funds after 2014.

(8) Exploiting the results of previously-initiated center-building efforts (when applicable)

**The reason why we believe that this WPI based on our existing FIRST program will succeed**

Our forward genetic screening of mutagenized mice for sleep/wake abnormalities, which is enabled by the FIRST program, has been going on smoothly with promising positive results. Our medicinal chemistry efforts to develop orexin receptor agonists have been progressing as well. These large-scale projects will yield lots of “seeds” in the near future, from which we will be able to develop multiple interdisciplinary lines of highly important inquiries. Our suite of cutting-edge equipment and experimental systems developed under the FIRST program constitute an ideal environment where the prospective top Principal Investigators of this WPI Center can productively explore their research ideas.

**Our prospects after the FIRST program**

Considering the level of competitive research funds acquired by the prospective Principal Investigators in the recent past, we expect that we together will be able to secure approximately the same level of external research funds after 2014.

Others

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 complete within this fiscal year. 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 paying the salaries of multiple Principal Investigators with the University’s budgets.

As for the “ripple effects,” we believe that the concept of creating at Tsukuba an organization, which is akin to small “departments” in the U.S. universities, as described in the prospective Center Director’s vision, will have 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 chairman has the authority to allocate the departmental 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 chairman, 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 the department would be allocated flexibly and dynamically, considering the laboratory's scale of funding, number of personnel, and facility requirements. (iv) A post-doctoral scientist who is deemed capable of conducting scientifically independent research will 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 the department will freely discuss science with each other, constantly seeking for opportunities for formal and informal cooperation.

#### **The prospective Center Director's assurance and commitment**

Since the start of the current FIRST program at Tsukuba, Yanagisawa has been spending about 50% of the year in Japan, while continuing to hold his UTSW and HHMI positions and operate his laboratory in Dallas. However, he intends to retire from the HHMI (his sole source of salary) as soon as possible, and will work full-time as the WPI Center Director, if this application is funded.

## 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

Date November 9, 2012

To MEXT

Host institution University of Tsukuba  
Name and title of head of host institution Nobuhiro YAMADA, President

Signature by \_\_\_\_\_  
On behalf of  
Nobuhiro Yamada  
President  
University of Tsukuba  
Japan

I confirm that the measures listed below will be taken faithfully if the "International Institute for Integrative Sleep Medicine" is adopted under the World Premier International Research Center Initiative (WPI).

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

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 will be 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 (provisional name) has been launched. The whole University will get 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.

Our candidate for center director, Dr. Masashi Yanagisawa, has been a professor at the University of Texas for over 20 years, and will use this experience in managing this center. By incessantly supporting his efforts, the University will realize the "new ventures for the university" that are demanded by tomorrow's society.

We will specify “International Institute for Integrative Sleep Medicine” for a Midterm Plan in the near future.

<Concrete Measures>

(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 the case of project exploiting previously-initiated center-building efforts, how it will assist the center in securing sufficient independent resources to continue to secure the same scale of the measured amount through independent resources after that funding eventually ends.

In order to manage this center and carry out research activities there, the University will give support as indicated below which will amount 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 will be maintained at the same level through 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) shall continue to give intensive support to make this an international center pioneering new fields, as one of the Organization’s strategic initiatives. Specifically, the Organization will support 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 is anticipated that an equivalent amount will be gained. Even after the completion in FY2014 of the FIRST program that founded this center, we anticipate that the center will have about 115 researchers who will gain at least the same level of funds as the previous year. The University will be providing full support for their applications for competitive external and internal research funds.
- 3) Support through handling of personnel expenses  
The personnel expenses of University faculty participating in this center will be treated as University personnel expenses for researchers.  
University staff (approximately 3 persons) will be assigned to carry out the chief administrative work of the center such as general affairs, accounting, and research funding. The expenses for this staff will be handled by considering them to be administrative staff participating in an administrative support division.
- 4) Support through supply of research space  
The University will use its good offices to facilitate the building of research facilities (more than 5,000m<sup>2</sup>) according to a plan that will give the center an outstanding research environment and distinctive tangible advantages.
- 5) Support for the use of research facilities  
Various core facilities will be 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 will be 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/her leadership, a system will be 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 will take necessary measures such as amending relevant regulations if needed. Further, the director will be supported by the administrative division established within this center which includes Professor Emeritus Katsutoshi Goto who has rich administrative experience such as the director of the Center for Tsukuba Advanced Research Alliance, administrative personnel dispatched from the University for support, and personnel recruited from outside the University. These personnel will supply the director with the information needed for him/her 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 (provisional name) has been 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 will be made within the University to support design of the organization of this center.

Further, after the establishment of this center, if persons from other institutes in the University assemble in this center as principal investigators, thorough adjustment will be made with those institutes in keeping with this center's status as a target for the Organization for the Support and Development of Strategic Initiatives.

Specifically, adjustment and support will be carried out so that there is no impediment to the research and education carried out by the institute in question; these support includes securing replacement personnel and taking measures to reduce administrative and educational work loads. Further, a place for interchanges with the researchers at this center will be created, so as to aid in the nurturing of outstanding new personnel.

- (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 shall be made an independent research organization reporting directly to the University President and kept separate from other research centers. University systems will be executed flexibly, making amendments and adjustments as necessary.

Specifically, English shall be the official language of the center, with the administrative tasks carried out in English and administrative documents made bilingual. Persons with high English proficiency will be recruited from within and outside the University, and further training will be provided to those persons after entering the center.

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 will be introduced.

Also, to deal with requests for flexible execution, improvement, or adjustment of systems in the center, the director will exercise 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 will use its good offices to the greatest extent to facilitate the building of research facilities according to a plan that will give 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, the center will be provided with all floors on the E Building of the University Hospital, which will be vacated by January, 2013 into the new ward building currently under construction. The center will continue to use the floors on the Health and Medical Science Innovation Laboratory that are currently occupied by the FIRST Program. Together, the center will be provided with more than 5,000 m<sup>2</sup> of research floor space. The Hospital E Building is located in close proximities to both the Innovation Building and the Laboratory Animal Resource Center, which should be highly advantageous for the center to facilitate its research. During the required renovation of the E Building, the center will be provided with temporary floors on the Laboratory of Advanced Research D.

The Research Facility Center for Science and Technology will assist persons wishing to use facilities in and outside the University, through the Open Facility function which is scheduled to start being offered sometime this fiscal year. Among these facilities are those for cutting-edge mass spectroscopy, super-high resolution ultrasound echo sonography for mice, and in vivo luminescence/fluorescence imaging system for mice. This function will be expanded in stages, and will make possible the use of the pioneering research facilities in the Tsukuba area.

Further, University of Tsukuba will provide university housing or satisfactory housing close to the University to researchers and administrative staff participating in this center, including foreign researchers. The University will also make 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.

- (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. Leona 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 will make international interactions a part of daily activities, and that will make 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 will 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

Name	Age	Current affiliation (organization, department)	Academic degree and current specialties	Notes
1 Masashi Yanagisawa*	52	University of Tsukuba, International Institute for Integrative Sleep Medicine	M.D.,Ph.D. Neuroscience, Pharmacology	
2 Hiromasa Funato*	43	University of Tsukuba, International Institute for Integrative Sleep Medicine	M.D.,Ph.D. Neuroscience	
3 Takeshi Sakurai*	48	Kanazawa University, Department of Physiology and Neuroscience	M.D.,Ph.D. Neuroscience	By the end of 2012
4 Yoshihiro Urade*	59	Osaka Bioscience Institute, Department of Molecular Behavioral Biology	Ph.D. Neuroscience, Biochemistry	By October 2013
5 Robert Greene*	62	University of Texas Southwestern Medical Center, Department of Psychiatry	M.D,Ph.D. Neuroscience	By October 2013
6 Qinghua Liu*	41	University of Texas Southwestern Medical Center, Department of Biochemistry	Ph.D. Biochemistry Molecular biology	By October 2013
7 Hiroshi Nagase*	65	University of Kitasato, Department of Medicinal Chemistry and School of Pharmacy	Ph.D. Medicinal Chemistry	By October 2013
8 Ichiyo Matsuzaki*	52	University of Tsukuba, Faculty of Medicine	M.D,Ph.D. Occupational Psychiatric Medicine, Space Medicine	
9 Hitoshi Shimano*	51	University of Tsukuba, Faculty of Medicine	M.D.,Ph.D. Endocrinology, Metabolism	
10 Junichi Hayashi*	63	University of Tsukuba, Faculty of Life and Environmental Sciences	Ph.D. Cell Biology	

**List of Principal Investigators**

Name	Age	Current affiliation (organization, department)	Academic degree and current specialties	Notes
11 Akiyoshi Fukamizu*	53	University of Tsukuba, Faculty of Life and Environmental Sciences	Ph.D. Molecular Biology	
12 Satoru Takahashi*	51	University of Tsukuba, Faculty of Medicine	M.D.,Ph.D. Developmental biology	
13 Tetsuo Shimizu*	59	Akita University Graduate School of Medicine, Department of Neuropsychiatry	M.D.,Ph.D. Psychiatry	satellite
14 Carla Green*	50	University of Texas Southwestern Medical Center, Department of Neuroscience	Ph.D. Neuroscience	satellite (overseas)
15 Joseph Takahashi*	61	University of Texas Southwestern Medicinal Center, Molecular Neurobiology and Genetics	Ph.D. Neuroscience	satellite (overseas)