

FY 2012 WPI Project Progress Report

World Premier International Research Center Initiative (WPI)

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

* Prepare this report based on the current (31 March 2013) situation of the WPI Center.

* Amounts of money are to be noted in yen in this report. When necessary to convert other currencies into yen, please give the exchange rate used.

Summary of center project progress

The aim of IIIS is to elucidate the fundamental mechanism of sleep/wake regulation by combining the cutting-edge methodologies of neuroscience, 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 the number of patients suffering from sleep disorders and associated diseases, and to contribute to an improvement of physical and mental health in today's aging society with a dwindling birth rate. An overview of the progress towards these goals follows below:

1. Establishment of the International Institute for Integrative Sleep Medicine (IIIS)
IIIS was established at the University of Tsukuba on December 1, 2012, with Dr. Masashi Yanagisawa appointed as Center Director.
2. Invitation of Principal Investigators (PIs)
Seven individuals have been offered positions as PIs. This includes 2 from the existing Center for Behavioral Molecular Genetics and 5 from within the University of Tsukuba campus.
3. Configuration of Center
In addition to the researchers, research assistants and office staff from the existing Center for Behavioral Molecular Genetics, 3 new researchers have been employed, bringing the total to 40 members. The proportion of women is 38%, while the proportion from overseas is 13%.
4. Collaborative Institutions
With the support of the University of Tsukuba Industry Relations and Technology Transfer Office, we have begun negotiating a joint research agreement with one of our satellites, University of Texas Southwestern Medical Center. It was decided to retain the support of an outside law firm (Oh-ebashi LPC & Partners), as the experience of the Industry Relations and Technology Office is limited for agreements with overseas institutions.
5. Research Support
As of the end of March 2013, our administrative staff is grouped under the administrative director and two associate administrative directors, with the 4 teams of general affairs/planning, accounting, research strategy & management, and

alliance & communication. Four new staff members that are proficient in English have been employed. In addition, we have contracted the Japan International Science and Technology Exchange Center (JISTEC) to provide daily life support services to our overseas researchers.

6. Outreach

On March 27, 2013, the 1st Annual IIIS Symposium was held at the Tsukuba International Congress Center, serving as our center's kick-off symposium. All of our principal investigators and junior principal investigators delivered lectures at the event, which welcomed about 190 participants. Including satellite-affiliated researchers, everyone was able to gather together during the event, which will become a place to reconfirm our joint research system in the future.

On Wednesday, February 13, 2013, the WPI-IIIS website was launched.

We held 13 seminars (IIIS Seminar Series) with invited researchers (both Japanese and overseas) in the fields of sleep and neuroscience (from December 2012 through the end of March 2013).

7. General/Environmental Improvements

We are currently planning to construct a new building (6 floors, 8,000 square meters of floor space) for IIIS within the medical sciences area of the University of Tsukuba campus. We have established a construction project secretariat within our administration, and aim for completion of the new building by March 2015. We are proceeding with the necessary preparations and adjustments for the design of the new facilities and equipment to be introduced.

We have secured an administrative office area (475 square meters) from the existing facilities (University of Tsukuba Hospital, E Building) to create a support system.

To provide laboratory space and research offices for the newly hired research groups 1,252 square meters of existing space was secured and refurbished (Project and Research Building, University of Tsukuba Hospital, E Building, Life Science Center of Tsukuba Advanced Research Alliance "LS-TARA Center"). Renovation of the Project and Research Building, in addition to LS-TARA Center was completed at the end of March, while it is scheduled for completion in the University of Tsukuba Hospital E Building in June. We also continue to make use of existing facilities (Health and Medical Science Innovation Laboratory, about 1,100 square meters, and the Laboratory Animal Resource Center, 418 square meters).

1. Summary of center project

<Plan at start of project>

Sleep is a remarkably universal phenomenon in the higher animal species, and its disturbances reduce mental and physical wellbeing. However, the function of sleep and the mechanism for sleep regulation still remain unknown; these questions are among the most important challenge in modern neuroscience. We gather globally prominent scientists from multiple research fields contributing to the neurobiology of sleep. They cooperate together to elucidate the fundamental principles of sleep/wake regulation, and develop new strategies to make diagnoses and treat sleep diseases as well as the closely associated metabolic and mental disorders.

<Results/progress/alternations from plan at start of project >

No changes to summary of center project.

2. Research fields

<Plan at start of project >

Sleep medicine

The research area consists of a fusion of neuroscience, medicine, pharmacology, chemistry and biology. 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.

<Results/progress/alternations from plan at start of project >

No changes to target research fields.

3. Research objectives

< Plan at start of project >

The research objectives that we seek to achieve are: 1) elucidation of the fundamental mechanisms of sleep/wake regulation, 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 regulation
[Research objectives to be accomplished by the end of the grant period]

<Results/progress/alternations from plan at start of project >

No changes to research objectives.

- 1.) Elucidation of the fundamental mechanisms of sleep/wake regulation
[Research objectives to be accomplished by the end of the grant period]

- Identification of new gene in sleep/wake regulation
- Elucidation of operating principles of neural networks regulating sleep/wake

Our current knowledge on sleep/wake regulation is actually quite limited when judged under the rigorous standards of today's neuroscience. Among the limited tidbits is the notion that the lateral hypothalamic orexin neurons and the wake-active monoaminergic and cholinergic neurons of the classical ascending activation system, together with the sleep-active GABAergic neurons of the preoptic hypothalamus, likely constitute important parts of the executive circuitry for sleep/wake switching. Orexin neurons are clearly important for the stability of the switch. We know that the sleep-inducing substance adenosine (which is blocked by caffeine) is importantly involved in the regulation of the "depths" of non-REM sleep. We know that these executive systems are powerfully governed by the circadian clock in the suprachiasmatic nucleus and by the presumed "sleep homeostat" somewhere in the brain. Overall, our current level of understanding is rudimentary at best. We 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.

2.) Elucidation of molecular pathogenesis of sleep disorders

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

- Elucidation of sleep/wake regulation in the brain and in associated peripheral organs
- Elucidation of intracellular events and molecular association of sleep/wake behavior in the body

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.

- Identification of new gene in sleep/wake regulation
- Elucidation of operating principles of neural networks regulating sleep/wake

[Results/progress until end of FY 2012]

Mutated mice created by insemination from wild-type female mice eggs and the sperm of a C57B/6J mouse that received randomly induced point mutation using ENU-based gene mutagenesis were screened for mice expressing an abnormality in sleep/wake regulation by performing EEG monitoring at the rate of 60 to 80 mice per week. Eight pedigrees of mice shown with a hereditary sleep abnormality have been established in our research so far, and we have succeeded in the chromosome mapping of two pedigrees. We are performing whole exome sequencing using next-generation DNA sequencing for pedigrees with sleep abnormalities. In FY 2013, we are expecting to be able to identify multiple genes responsible for variation in sleep abnormality.

2.) Elucidation of molecular pathogenesis of sleep disorders

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

- Elucidation of sleep/wake regulation in the brain and in associated peripheral organs
- Elucidation of intracellular events and molecular association of sleep/wake behavior in the body

[Results/progress until end of FY 2012]

The awakening effect of caffeine was found to be lost by deleting adenosine A2A receptors selectively in the nucleus accumbens of the mouse (NAc) shell. It was shown that A2A receptors play an important function in the regulation of sleep/wake.

<p>3.) Development of new treatment methods for sleep disorders [Research objectives to be accomplished by the end of the grant period]</p> <ul style="list-style-type: none"> ● Development of sleep disorder therapy drug-candidate proceeding to clinical trial stage ● Development of multi-faceted "Good Sleep" program that does not use drugs for the prevention of sleep disorders was based on basic and clinical research <p>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 of sleep disorders 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.</p>	<p>3.) Development of new treatment methods for sleep disorders [Research objectives to be accomplished by the end of the grant period]</p> <ul style="list-style-type: none"> ● Development of sleep disorder therapy drug-candidate proceeding to clinical trial stage ● Development of multi-faceted "Good Sleep" program that does not use drugs for the prevention of sleep disorders was based on basic and clinical research <p>[Results/progress until end of FY 2012] Multiple hit compounds were obtained when we conducted a high-throughput screening of 250,000 varieties of low-molecular-weight compounds to index the agonist activity of orexin receptors. We are continuing structural modifications and conversion of the basic structure, based on the structure of hit compounds. In the previous fiscal year, compounds showing agonist activity of type 2 orexin receptor at 1μM had been found. However, by the end of FY 2012, compounds showing activity at 100 nM were obtained with continued optimization including the separation of optical isomers.</p>
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<p>4. Management</p>	
<p><Plan at start of project > 1) Composition of administrative staff</p> <p><i>1. Composition of administrative staff</i></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.</p> <ul style="list-style-type: none"> • General affairs section (5 staff members) 	<p><Results/progress/alternations from plan at start of project > 1) Composition of administrative staff</p> <p>The administration is composed of the administrative director and two associate administrative directors that serve as supervisors for each of the two units that have been established: Management Strategy & Planning Unit and Research Strategy & Communication Unit. Within the Management Strategy & Planning Unit are the General Affairs and Accounting teams, where staff members with ample administrative experience have been placed. The Research Strategy and Communication houses the Research Strategy & Management Team in addition to the Alliance & Communication</p>

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,

Team. This unit has a diverse group of team members that includes private sector experience, PhDs and native English ability. All members hired into this team have proficient command of English. We have planned for 6 out of 18 of our administrative staff members to be bilingual by April 2013.

We have also concluded a contract with the Japan International Science and Technology Exchange Center (JISTEC) to commission their support services for our overseas researchers.

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.

2) 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.

2) Decision-making system

For administrative management within the center, all decision-making is done in accordance to the Center Director's top-down approach. So that the will of the Center Director will take effect quickly, organizational bylaws and other related regulations were enacted. However, we have also established a system to deliberate about research plans, institutional organization/administration, etc., by introducing a steering committee within IIIS. In addition, PI meetings will also be held, whereby an opportunity is provided to debate and exchange opinions with the Center Director and other PIs.

3) Allocation of authority between 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.

3) Allocation of authority between center director and host institution

Proceeding as initially planned.

5. Researchers and center staffs

i) "Core" to be established within host institution

Principal investigators

	At beginning	Final goal (Date: month, year)	Results at end of FY 2012	Results at end of April 2013
Researchers from within host institution	7	7	7	7
Foreign researchers invited from abroad	0	4	0	1
Researchers invited from other Japanese institutions	0	4	0	1
Total principal investigators	7	15	7	9

All members

- In the "Researchers" column, put the number and percentage of overseas researchers in the < > brackets and the number and percentage of female researchers in the [] brackets.

- In the "Administrative staffs" column, put the number and percentage of bilingual staffs in the () brackets.

	At beginning	Final goal (Date: 3, 2015)	Results at end of FY 2012	Results at end of April 2013
Researchers	41 <1, 2%> [8, 20%]	115 <35, 30%> [35, 30%]	16 <2, 13%> [6, 38%]	30 <5, 17%> [10, 33%]
Principal investigators	7 <1, 14%> [0, 0%]	15 <5, 33%> [1, 7%]	7 <1, 14%> [0, 0%]	9 <2, 22%> [0, 0%]
Other researchers	34 <0, 0%> [8, 24%]	100 <30, 30%> [34, 34%]	9 <1, 11%> [6, 67%]	21 <3, 14%> [10, 48%]
Research support staffs	17	40	8	10
Administrative staffs	14	14	16 (6, 38%)	18 (6, 33%)
Total	72	169	40	58

ii) Satellites

<Plan at start of project >

Institution (1) University of Texas Southwestern Medical Center

-Role

Joint research on the relationship between sleep/wake regulation and circadian rhythm, and the ENU Project (molecular genetic research)

-Personnel composition and structure

Carla Green, Joseph Takahashi

-Collaborative framework

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.

Institution (2) Akita University

-Role

Joint research in translational research

-Personnel composition and structure

Tetsuo Shimizu, Takashi Kanbayashi

-Collaborative framework

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

<Results/progress/alternations from plan at start of project>

Institution (1) University of Texas Southwestern Medical Center

-Role

Joint research on the relationship between sleep/wake regulation and circadian rhythm, and the ENU Project (molecular genetic research)

-Personnel composition and structure

Carla Green, Joseph Takahashi, Masashi Yanagisawa

-Collaborative framework

The laboratory of Masashi Yanagisawa in University of Texas Southwestern Medical Center (UTSW Yanagisawa Lab) has been conducting joint research on the transfer methods of ENU screenings, and from November of last year began whole exome sequencing analysis of mice pedigrees showing sleep/wake abnormalities. The exome sequencing analysis is conducted in collaboration with the Next-Generation DNA Sequencing Core facility located in UTSW, and a collaborative structure with the researchers and core facility has been formed that is capable of identifying genes responsible for mutation within three months after chromosomal mapping. Satellite activities of UTSW Yanagisawa Lab have become indispensable for the success of forward genetics research. So in addition to Dr. Takahashi and Dr. Green, 3 labs from UTSW, including that of Dr. Yanagisawa will serve as satellites for research cooperation.

Institution (2) Akita University

-Role

Joint research in translational research

-Personnel composition and structure

Tetsuo Shimizu, Takashi Kanbayashi

-Collaborative framework

As planned, we are preparing the conclusion of a collaboration research agreement and research plan in order to set up our largest satellite in Akita University, which is the only place for the clinical study of orexin in Japan.

<p>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.</p>	
<p>iii) Partner institutions < Plan at start of project > <u>Institution (1)</u> RIKEN BioResource Center, Tsukuba -Role Joint research in ENU screening</p> <p>-Personnel composition and structure Shigeharu Wakana</p> <p>-Collaborative framework 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.</p>	<p><Results/progress/alternations from plan at start of project> <u>Institution (1)</u> RIKEN BioResource Center, Tsukuba -Role Joint research in ENU screening</p> <p>-Personnel composition and structure Shigeharu Wakana</p> <p>-Collaborative framework As planned, we are conducting joint research through use of ENU screenings in order to identify sleep/wake regulatory genes</p>

<u>Institution (2)</u>	<u>Institution (2)</u> Niigata University -Role Joint research for the development of genetically modified mice -Personnel composition and structure Kenji Sakimura -Collaborative framework There was previous collaboration between Kenji Sakimura of the Brain Research Institute at Niigata University during 2010-2011 on the preparation of genetically engineered mice. As the prospect for identifying the gene responsible for sleep-wake abnormalities has passed, we will resume joint research to create mice harboring the genes with additional mutations. In addition to drawing up a research plan, we are also considering the conclusion of a joint research agreement.
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6. Summary of center's research environment

< Plan at start of project >

1) Environment in which researchers can devote themselves to their research

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,

<Results/progress/alternations from plan at start of project>

1) Environment in which researchers can devote themselves to their research

The administration was established under the direction of an administrative director that is familiar with both science and business operations so that researchers will be able to concentrate on research. Staff members consist not only of those familiar with campus operations, but also those with diverse backgrounds, including private sector experience, PhDs and native English. Seminars, symposia and the launch of our website were all carried out without bothering most of our researchers.

To support the daily lives of our researchers, we have contracted the Japan International Science and Technology Exchange Center (JISTEC).

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.

2) Startup research funding

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.

3) Postdoctoral positions through open international solicitations

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.

2) Startup research funding

Research start-up funds were offered to PIs invited from outside of the University of Tsukuba, along with Junior PIs. These funds are decided by the Center Director, based on the budget plan.

3) Postdoctoral positions through open international solicitations

We are furthering recruiting efforts by using sites such as Naturejobs.com, etc., in addition to our IIIS website, and having the Center Director and PIs make use of their own international networks.

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 premiere status.

4) 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.

5) Rigorous system for evaluating research and system of merit-based compensation

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

4) Administrative personnel who can facilitate the use of English in the work process

The Research Strategy & Communication Unit is responsible for business that is mainly related to science and general operations related to English. Communication in English is possible with all members. In addition, we plan to hire only bilingual executive assistants for all PIs.

5) Rigorous system for evaluating research and system of merit-based compensation

Researcher evaluations will be conducted at the beginning of the fiscal year. Salaries of administrative staff will be based on the

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.

6) 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 m² 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

opinions of the Administrative Director and then decided by the Center Director. Salaries of researchers will be determined based on the former salary and research results of researchers invited from other institutions.

6) Equipment and facilities, including laboratory space, appropriate to a top world-level research center

We are proceeding with the construction of a new research building that will serve as the core facility for IIIS to be completed by the end of FY 2014.

The new building will be approximately 8,000 square meters and constructed in reference to world-class research centers, while fully reflecting the intentions of world-class researchers. It will be maintained as an appropriate facility for original research activities to "elucidate the fundamental mechanism of sleep/wakefulness". Specifically, plans for experimental facilities are in place whereby 1/3 of the total floor space will be dedicated to animal facilities suited for the latest sleep & behavior analysis and optogenetics of multiple mouse pedigrees. In addition, cages will be installed for a rearing facility that allows for sufficient breeding capacity (5,000 cages).

The new location is in the northern part of the University of Tsukuba

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.

7) International research conferences or symposiums held regularly to bring world's leading researchers together

medical sciences area. There is a reservoir (Kasuga Pond) within the green space of the conservation area that comes in contact with the proposed building site on its east bank, where it is scheduled to be diverted. It will be adjacent to the Laboratory Animal Resource Center, where collaboration is essential. The design concept sandwiches together the nature reserve with this lush, green space and reservoir, and the medical sciences area to interface with people and nature. Fusing together various different areas of research, this is considered an optimal environment for research into the prevention and clarification of patient conditions and treatment methods for sleep disorders and associated diseases.

While the new building is being constructed, the current research site, Health and Medical Science Innovation Laboratory, will serve as the research core. At the same time, laboratories located in the Project and Research Building and LS-TARA Center will be utilized so that full-scale research activities can proceed early on.

7) International research conferences or symposiums held regularly to bring world's leading researchers together

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.

8) Other measures, if any

The University Research Administrator (URA) office of the University of Tsukuba (director: vice president in charge of research), which has been established as a part of the "Global 30" initiative by the MEXT, 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 3rd and 4th 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.

1. International Symposium
The 1st Annual IIIS Symposium
Date: March 27, 2013
Place: Tsukuba International Congress Center
Participants: about 190
Outline: launch of kick-off symposium with all PIs gathered together.

2. International Seminars
We conducted 13 presentations (IIIS Seminar Series) with invited researchers (both Japanese and overseas) in the fields of sleep and neuroscience (from December 2012 through the end of March 2013).

8) Other measures, if any

1. IIIS website launched
<http://wpi-iiis.tsukuba.ac.jp>
2. In addition to participating in seminars hosted by URA, we have exchanged information and opinions in liaison conferences.
3. The following image is the logo for IIIS:



INTERNATIONAL INSTITUTE FOR INTEGRATIVE
SLEEP MEDICINE

7. Criteria and methods used to evaluate center's global standing

<p>< Plan at start of project ></p> <ol style="list-style-type: none">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.	<p><Current assessment></p> <p>Because 1. and 2. for the "Plan at start of project" are for the medium to long-term, they are not yet suitable for evaluation as this is the initial year for IIIS. So for the current short-term assessment, we will report on the publications by PIs in the 2012 fiscal year below:</p> <p>For all of our PIs together, 54 peer-reviewed articles and 22 books were announced, for a total of 76 publications. In particular, the work from Junichi Hayashi's lab [Hashizume O, et al. Proc. Natl. Acad. Sci. USA 109: 10528-10533(2012)] and that of Akiyoshi Fukamizu's lab [Okamura E, et al. Mol. Cell. Biol. 33, 858-871 (2013)], etc. were published in journals with a high impact factor. In the 2013 fiscal year and the four years leading up to it from 2009 when the FIRST Program was started as the existing organization prior to IIIS, announcements of many research results have been possible.</p> <p>In addition, teams set within IIIS are planning to vigorously apply for external funding.</p>
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8. Securing competitive research funding

<p><Plan at start of project ></p> <p>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.</p>	<p><Results/progress/alternations from plan at start of project></p> <p>FY 2012: 6,863,483 USD (686,348,300 JPY) (exchange rate of \$1 = 100 JPY)</p>
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9. Other important measures taken to create a world premier international research center

<p><Plan at start of project ></p> <p>Center Director Yanagisawa intends to retire from HHMI promptly after the application is funded.</p>	<p><Results/progress/alternations from plan at start of project></p> <p>With the progress made in the forward genetics collaboration among RIKEN, IIIS and UTSW Yanagisawa Lab, the importance of UTSW Yanagisawa Lab as a satellite has soared. For this reason, we would like to maintain the Yanagisawa Lab and request a grace period for the retirement from HHMI. Dr. Yanagisawa is eligible for the 5-year phase out retirement program, so at next year's scheduled contract renewal for HHMI Investigator, we hope he is allowed to apply for the 5 year-phase out program.</p>
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10. Host institution's commitment

<p><Plan at start of project ></p> <p>-Provision in host institution's mid-to-long-term plan</p> <p>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."</p> <p>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."</p> <p>Therefore, the World Premier International Research Center Initiative (WPI) is in complete agreement with the University's Midterm Goals and Midterm Plan.</p> <p>Further, as the strategy to achieve the University's goals regarding systems to carry out research, the Midterm Plan stipulates that</p>	<p><Results/progress/alternations from plan at start of project></p> <p>-Provision in host institution's mid-to-long-term plan</p> <p>For this fiscal year, the University of Tsukuba specified IIIS in the "mid-term plan".</p>
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“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.

-Concrete Measures

(1) Competitive grants obtained by researchers participating in the project and in-kind contributions, etc.

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.

-Concrete Measures

(1) Competitive grants obtained by researchers participating in the project and in-kind contributions, etc.

A strategic new initiative was launched targeting international centers driving new cutting-edge research by the University of Tsukuba’s Organization for the Support and Development of Strategic Initiatives (composed of university president and vice president) in which a support program has been established to provide continuous support to IIIS. Specifically, it is receiving 10 million yen per year for support with center

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 5,000m²) 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).

activities.

As of January 1, 2013, we have two university officials in the general affairs and accounting division, with one additional official scheduled to be placed by April 2013.

To provide our researchers with a suitable environment where they can all work together under one roof, we have secured a site for the construction of a new 6-story building (8,000 square meters). In addition, we have provided our members with 1,252 square meters of existing space to use as research facilities until the new building is complete (including the Project and Research Building, University of Tsukuba Hospital, E Building, Life Science Center of Tsukuba Advanced Research Alliance "LS-TARA Center"). We also continue to make use of core existing facilities (Health and Medical Science Innovation Laboratory, about 1,100 square meters, and the Laboratory Animal Resource Center, 418 square meters).

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

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

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

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

IIIS does not belong to any organizational hierarchy, having been established as an independent organization directly under the university president. The Center Director has full authority to run the center, including with decisions on important matters such as the budget and personnel.

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

After the establishment of IIIS, regular liaison conferences with the vice president of the University of Tsukuba in charge of research have been held to allow for coordination and exchange of information inside the campus.

We are quickly working to establish a system to implement close-knit joint research with our researchers. In the future, changes to the center will be

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 workloads. 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) Revamping host institution's internal systems to allow introducing of 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

considered as necessary.

(4) Revamping host institution's internal systems to allow introducing of new management methods (e.g., English-language environment, merit-based pay, top-down decision making) unfettered by conventional modes of operation

Under the present salary system, payment can only be made at an hourly rate for principal investigators from UTSW to be invited as visiting professors; therefore, we have started consultations with the human resource department to be able to create contracts whereby payments will be made under the annual salary system.

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) Accommodation of center's requirements for infrastructural support (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 m² 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

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

We are proceeding with the construction of a new research building that will serve as the core facility for IIIS to be completed by the end of FY 2014.

The new building will be approximately 8,000 square meters and constructed in reference to world-class research centers, while fully reflecting the intentions of world-class researchers. It will be maintained as an appropriate facility to for original research activities to "elucidate the fundamental mechanism of sleep/wakefulness". Specifically, plans for experimental facilities are in place whereby 1/3 of the total floor space will be dedicated to animal facilities suited for the latest sleep & behavior analysis and optogenetics of multiple mouse pedigrees. In addition, cages will be installed for a rearing facility that allows for sufficient breeding capacity (5,000 cages).

The new location is in the northern part of the University of Tsukuba medical sciences area. There is a reservoir (Kasuga Pond) within the green space of the conservation area that comes in contact with the proposed building site on its east bank, where it is scheduled to be diverted. It will be adjacent to the Laboratory Animal Resource Center, where collaboration is essential. The design concept sandwiches together the nature reserve with this lush, green space and reservoir, and the medical sciences area to interface with people and nature. Fusing together various different areas of research, this is considered an optimal environment for research into the prevention and clarification of patient conditions and treatment methods for sleep disorders and associated

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) Support for other types of assistance

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.

diseases.

While the new building is being constructed, the current research site, Health and Medical Science Innovation Laboratory, will serve as the research core. At the same time, laboratories located in the Project and Research Building and LS-TARA Center will be utilized so that full-scale research activities can proceed early on.

(6) Support for other types of assistance

We have been actively making preparations to conclude joint research agreements with the assistance of URA and the Industry Relations and Technology Transfer Office.

11. Efforts to improve points indicated as requiring improvement in application review and results of such efforts

- Major points to be improved

• There is the issue of how to translate animal studies into humans. More concrete strategy seems needed.

- Efforts to improve them and results

*If you have already described these in other parts of this report, please indicate where for reference.

• There is the issue of how to translate animal studies into humans. More concrete strategy seems needed.

In order to bridge the basic research of IIIS into clinical studies, Akita University will play an important role as our satellite. Prof. Tetsuo Shimizu, Chair of the Department of Neuropsychiatry at Akita University Graduate School of Medicine, and his research group have a proven track record of clinical research dealing mainly with sleep disorders focusing on hypersomnia, such as narcolepsy, that is the most expansive in Japan. The research group has accumulated clinical information from numerous cases, along with bioresources, including cerebrospinal fluid, blood and DNA. The group in Akita University will be positioned as a hub to bridge the results of IIIS basic research with medicine & medical science.

One example of a collaborative research program we are currently considering is translational medicine (TM) research of biomarkers related to sleep/wake abnormalities. At IIIS, using molecular genetic techniques we have been searching for genes important to sleep/wake regulation. Recently, we have succeeded in the identification of two genes. Continuing the gene search into the future, we may find a mouse gene suitable as a biomarker of sleep/wake regulation abnormality. When the mouse biomarker is found, Prof. Shimizu's TM research using bioresources may let us discover clinical biomarkers. In addition, clinical trials sponsored by the investigator or clinical research could be conducted by his group in collaboration with IIIS. There is currently a medicinal chemistry research group at IIIS focusing on orexin agonist drug discovery research. With the creation of a lead compound, the clinical trial or clinical research could be carried out to establish a clinical proof of concept.

Meanwhile, collaboration is ongoing with Prof. Ichiyo Matsuzaki, who is serving as one of our principal investigators at the University of Tsukuba, and his Occupational Psychiatry / Space Medicine Group. We plan to further collaborate on research dealing with changes in sleep in a long-term closed environment. In today's society with shift and night time hours at work, etc., opportunities to engage in behavior that go against circadian rhythm are plentiful. And when there is a lack of sleep, the possibility of an increase in mental health-related diseases becomes high. Through this collaborative research, we are aiming to directly solve the problems facing today's society, by turning our research results into a social contribution.

Furthermore, potential clinical research on human subjects is being considered in our collaborations with Prof. Makoto Satoh (Faculty of Medicine) and Prof. Kumpei Tokuyama (Faculty of Health and Sport Sciences). With

<p>•Clinical or human research should be more strengthened. In this respect, international collaboration with established sleep laboratories is very important.</p> <p>• Explanation on collaborations among PIs lacks details. It is not totally clear that the group will cohere and attain scale effects. The plans for using the WPI to springboard to a much greater impact were not well stated.</p>	<p>Prof. Satoh as the leader for the Sleep-disordered Breathing Diagnosis Group, medical examination and treatment mainly for Sleep Apnea Syndrome (SAS) is ongoing, in addition to research related to clinical treatment, early detection and prevention of sleep disorders. Also, Prof. Tokuyama is conducting research on energy metabolism, including during sleep. His group maintains the most accurate human calorimeter in the world that can be used to measure energy metabolism from oxygen and carbon dioxide production levels without needing a mask to collect expired gas. By preparing an electroencephalograph, we would like to clarify how energy metabolic changes, etc., occur during sleep in the future.</p> <p>In addition, we are planning for collaborative research and development with companies, etc., involved in the development of sleep timers. With the health data that Prof. Tokuyama's research group has accumulated (sleep, body weight, blood pressure, activity level), and the more than 20 years of survey data collected by Prof. Matsuzaki's group on work environment including sleep, we envisage a cohort study to continue with further analysis.</p> <p>•Clinical or human research should be more strengthened. In this respect, international collaboration with established sleep laboratories is very important.</p> <p>We would like to plan for collaborative research, exchange of researchers, solicitation of invitations for speakerships at our symposia, and exchange of research information with the already established sleep research institutes at Stanford University School of Medicine, the Center for Sleep Sciences and Medicine and the Center of Excellence for the Diagnosis and Treatment of Sleep Disorders, in addition to the Penn Comprehensive Neuroscience Center and the Center for Sleep and Circadian Neurobiology at the Pennsylvania School of Medicine. In addition, we hope to engage in collaborative research with the CNRS (Centre national de la recherche scientifique) of France.</p> <p>• Explanation on collaborations among PIs lacks details. It is not totally clear that the group will cohere and attain scale effects. The plans for using the WPI to springboard to a much greater impact were not well stated.</p> <p>We are considering a joint research theme for the cooperation with our Collaborative Principal Investigators at the University of Tsukuba (Prof. Shimano, Prof. Shimizu, Prof. Hayashi, Prof. Matsuzaki, and Prof. Takahashi).</p>
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•The proposal needs to be clearer in the end goal of the WPI funding. Even the fundamental part of research may take easily more than 10 years.

Prof. Shimano's group is investigating the relationship between sleep and metabolic syndrome from the aspects of transcriptional regulation and lipid metabolism. Abnormalities of fatty acid composition have been found to exert a significant influence on the brain, and it is expected that the collaboration between Shimano Group and the IIIS core members of neuroscientists could provide a new insight on the lipid metabolism in the brain.

Fukamizu Group is preparing to begin a study with a pregnant mouse serving as the model to study the effects on sleep during pregnancy.

Junichi Hayashi Group is beginning to investigate changes in sleep of mice with abnormalities in the mitochondria, the organ that performs intracellular energy production. Elucidation of the mechanism will take place as soon as the mice with sleep/wake regulation abnormalities are found.

As described above, we are planning to examine the changes in the sleep of people in a long-term closed environment through collaboration with Prof. Matsuzaki.

Satoru Takahashi, Director of the Laboratory Animal Resource Center, and his group have been in close collaboration in the past as well as with current research on the management and production of transgenic mice. We will further conduct collaborative research concerning the gene responsible for sleep/wake abnormalities along with validation of the responsible gene mutation.

Also, with the purpose of exchanging information and opinions, we will hold regular IIIS meetings with all members participating. By allowing a lively exchange of views between our research groups, we expect that many ideas for collaborative research will be born through such kind of brainstorming.

•The proposal needs to be clearer in the end goal of the WPI funding. Even the fundamental part of research may take easily more than 10 years.

While the meaning and regulatory mechanism of sleep are still unknown, the elucidation of the mystery surrounding sleep is one of the most important issues of modern neuroscience. The goal of IIIS is to achieve a breakthrough on this essential problem. Of course, this is a long-term target. As pointed out, we suspect that it will take more than 10 years to achieve the goal.

•The institutional support is not that impressive. How is the university committed to the program and wishes to support it?

However, the other goal of IIIS is to develop new treatments for diseases related to sleep disorders, which could be conducted in parallel to the central mission even before the full elucidation of the mystery surrounding sleep. What is needed first in order to start the drug discovery research is to identify target candidates (gene = protein molecule) that possess suitable (druggable) properties. The research that aims to unravel the mystery surrounding sleep, as listed above allowed us to discover these target candidates as byproducts. By identifying multiple genes critical to sleep/wake regulation, we expect to be able to discover good target candidates such as enzymes, receptors, secreted peptides/proteins, or ion channels.

The orexin receptor is the target candidate Center Director Yanagisawa found from his previous research on orphan receptors. Focusing on it as the first example of a target candidate, IIIS is commencing drug discovery research. In the future, we plan for the development of new therapies by expanding drug discovery research for target candidates to be identified in the course of research aiming to elucidate the mystery surrounding sleep.

Drug discovery research and continued non-clinical development, along with eventual clinical trials require 5-10 years to complete. In addition, as research and development progress, the necessary funding also increases rapidly, making it impossible for IIIS to complete development of a treatment/drug. The goal of IIIS is thus to establish Proof of Concept (POC) for a target candidate with a lead compound for the drug. When we are able to show the POC, it will enable us to license the lead to a bio-venture or a pharmaceutical company for further development. This will make it possible to contribute to the enhancement of world health, which is the ultimate goal of IIIS.

•The institutional support is not that impressive. How is the university committed to the program and wishes to support it?

Under the leadership of the University of Tsukuba President, the International Institute for Integrative Sleep Medicine (IIIS) will receive total support in order to fulfill its role as a World Premier International Research Center. After receiving the tentative decision for WPI selection in October 2012, procedures for establishment of IIIS were launched. On December 1, 2012, IIIS was inaugurated, together with being placed into the Support Program of the Organization for the Support and Development of Strategic Initiatives, headed by the university president. The program is supported proactively through

assistance and coordination with the vice president in charge of research.

Specifically the university is planning and executing a multi-pronged support system that includes assistance with financial affairs, improvement of center management, provision of research facilities and research activities.

The university's Organization for the Support and Development of Strategic Initiatives already provides the operating costs for this center, with 10 million yen each fiscal year allocated for operating costs. In addition to this funding, 3 university staff members have been placed at IIIS.

With the aim of flexible operation, improvement and maintenance of the university system, IIIS was positioned as a research institute that is independent from other research organizations on campus (established on December 1, 2012), with special measures available that are separate from the personnel rules of the university allowing for personnel to be hired quickly and efficiently.

Already, space has been allocated for IIIS in the University of Tsukuba Hospital E Building, Project and Research Building, Life Science Center of Tsukuba Advanced Research Alliance C Building and the Health and Medical Science Innovation Laboratory. With the goal of developing world-class facilities that boast high standards for research, along with creating an environment where globally prominent researchers can perform state-of-the-art research, we plan to construct a new building that is 8,000 square meters in area adjacent to the Laboratory Animal Resource Center (the fiscal 2012 supplementary budget: 6,000 square meters + budget of the university: 2,000 square meters). Further, the Research Facility Center for Science and Technology, an open facility function in the university, provides IIIS with access to additional research facilities, including mass spectrum, ultrasound imaging system for small animals and optical imaging equipment for small animals.

The Industry Relations and Technology Transfer Office provides IIIS with support for negotiation and conclusion of collaboration research agreements as well as material transfer agreements (MTA), which are vital to raise the profile of the distinguished research results at IIIS. In the future, together with taking care of procedures and management of patent applications, the Industry Relations and Technology Transfer Office will be providing its comprehensive support and knowhow of recruiting competent researchers

•It is unclear if the center is able to earmark enough amount of fund. In addition to receiving fund from private sector, efforts to get it from other research programs might be needed.

and executing collaboration research agreements between satellite schools. As for external funding, the University of Tsukuba's Research Administration Office (URA) is cooperating with IIIS administration to provide additional support, while we work towards providing all competitive funding information and university regulations relating to research in English.

The University of Tsukuba is taking full responsibility under the leadership of the university president to ensure IIIS has total support in order to become a true "World Premier International Research Center", taking advantage of the know-how of past achievements and utilizing the full extent of the resource base available for this center.

•It is unclear if the center is able to earmark enough amount of fund. In addition to receiving fund from private sector, efforts to get it from other research programs might be needed.

The majority of the researchers invited from outside the university and employed from April 1, 2013 have received grants-in-aid for scientific research. Funds of about 10 million yen have been newly transferred to IIIS. In addition, about 3 million yen has been awarded from private sector grants.

Also, we plan to aggressively apply for new competitive external funds. On a case-by-case basis, we consider our strategy for applications, and advance application work after holding several preparatory meetings in advance of upcoming deadlines. For FY 2014, we aim to acquire 140 million yen. To assist with this goal, the Research Strategy & Communication Unit in the administration division has placed a person exclusively in charge of external funds. External funding application information is collected and in-depth advice is being offered on application content. In the three months prior to June, we have already submitted 4 applications for external funds among government departments and 6 applications for private grants. In addition, we are planning to apply for the COE Graduate Center Program of the Ministry of Education, Culture, Sports, Science and Technology-Japan.

Furthermore, we are sounding out a few new projects for research collaboration with private companies with which the researchers invited from outside the university had previously engaged in collaborative research. We plan also to actively seek funding from such companies.

12. FY 2012 funding

(the exchange rate used: 100)

i) Overall project funding

Ten thousand dollars

Cost Items	Details	Costs (10,000 dollars)
Personnel	Center director and Administrative director	4
	Principal investigators (5. of persons):	8
	Other researchers (3. of persons):	3
	Administrative staffs (3. of persons):	1
	Total	16
Project activities	Gratuities and honoraria paid to Administrative director (1. of persons):	2
	Cost of dispatching workers (4. of persons):	3
	Research startup cost :	31
	Cost of international symposiums (1. of symposiums):	1
	Cost of consumables	2
	Total	39
Travel	Domestic travel costs	1
	Overseas travel costs	3
	Total	4
Equipment	Depreciation of buildings	8
	Depreciation of equipment	268
	Total	276
Other research projects	Endowment	12
	Total	12
	Total	347

WPI grant for FY 2012

Costs of establishing and maintaining facilities in FY 2012	8
Repairing facilities (Number of facilities:1 , 253 m ²)	Costs paid: 2
Others	6
Cost of equipment procured in FY 2012	268
ElectroSpray Ionization real time direct Time-of-flight mass spectrometry: TOF-MS	29
Name of equipment: Fourier transform Magnetic Resonance Imaging System	24
Number of units: Costs paid:	
Name of equipment: Crystal X-ray Diffractometer	32
Number of units: Costs paid:	
Others	183

ii) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (10,000 dollars)
Personnel		/
	Total	
Project activities		0
Travel		0
Equipment		0
Other research projects		0
	Total	0