

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

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

1) Project summary

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

2) Mission statement and/or center's identity

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

3) Research fields

Name of the target research field Sleep science

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

Importance of the target research field

Sleep is a behavior that everyone experiences daily and it takes up as much as one third of one's entire lifetime. While sleep has been a black box stubbornly resisting scientists' challenges, its medical and social importance is very clear. Healthy sleep is necessary for maintaining our mind and body fitness; lack of sound sleep not only causes a reduction in higher brain functions including memory and decision making, but also increase the risk of mood disorders such as depression. The society demands the development of strategies to remedy sleep disorders and associated diseases.

Research trend of this field

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

Reasons why the project fit for this call for proposals

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

4) Research objectives

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

5) Outline of management

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

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

Decision-making system

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

Allocation of authority between the center director and host institution

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

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

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

7) Outline of research environment

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

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

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

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

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

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

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

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

9) Securing research funding

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

10) Appropriations plan

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

(Exchange Rate: JPY/USD=100)

11) Summary of host institution's commitment

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

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

Concrete Measures

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