

Center Director's Vision

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- Background, Targets and Objectives

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

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

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

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

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

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

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

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

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

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

- Fusion of neuroscience and medicinal chemistry

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

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

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

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

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

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

- Contributing to the Society

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

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

- Concluding remark

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