IIIS

INTERNATIONAL INSTITUTE FOR INTEGRATIVE SLEEP MEDICINE
UNIVERSITY OF TSUKUBA

Director's message

We aim to solve one of the biggest black boxes of today's neuroscience

Our discovery of the neuropeptide orexin and its prominent role in sleep/wake regulation has generated a highly active research field in neurobiology of sleep. However, the fundamental governing principle for the regulation of sleep pressure, e.g., the question of (1) what the neural substrate for "sleepiness" is, (2) why we have to sleep, remains a mystery. Indeed, this is one of the biggest mysteries in today's neuroscience.

Based on my own 24-year experience as a PI in the US, and by learning from the merits of US academia while retaining the merits of Japanese traditions, IIIS provides a scientific culture and environment that strongly encourages all members, regardless of career stage, to initiate and continue truly groundbraking studies.

Masashi Yanagisawa
Director

World-class institute for sleep medicine, aiming to solve the mechanism of sleep/wakefulness by conducting basic to translational research

About IIIS

We spend nearly one-third of our lives asleep. However, the regulation and function of sleep remain unclear. The importance of sleep is very clear because the loss of sound sleep impairs daytime performance and increases the risk of physical and mental disorders. Deficiencies of sleep cause a huge economic loss, burdening the Japanese society about 1.5 billion yen per year. IIIS approaches this social problem through interdisciplinary sleep science, combining with basic neurobiology, pharmaceutical chemistry, and experimental medicine.

IIIS is the world's premier institute aiming to elucidate the fundamental principles of sleep/wake biology, develop new strategies to diagnose, prevent sleep disorders, and contribute to promoting well-being health through research activities.

Feature of the Institute

Based on Dr. Yanagisawa's more than 20 years experience as a PI at the University of Texas Southwestern Medical Center, IIIS has established the best and unique sleep research center in Japan, by learning from the merits of the U.S.-style academic "department." IIIS has created a free and vigorous atmosphere emphasizing: (i) flexible and timely appointments of independent PIs regardless of their age and career stage, with a necessary startup package (e.g. funding, personnel and space); (ii) a flexible and dynamic allocation of floor space for each laboratory to facilitate free and open communications; and (iii) sharing of major facilities and capital equipment among laboratories. IIIS manages the organization so that all researchers and students can vigorously communicate and maximize their potentials.

MISSION

To uncover the mystery of sleep, and to solve sleep-related social problems

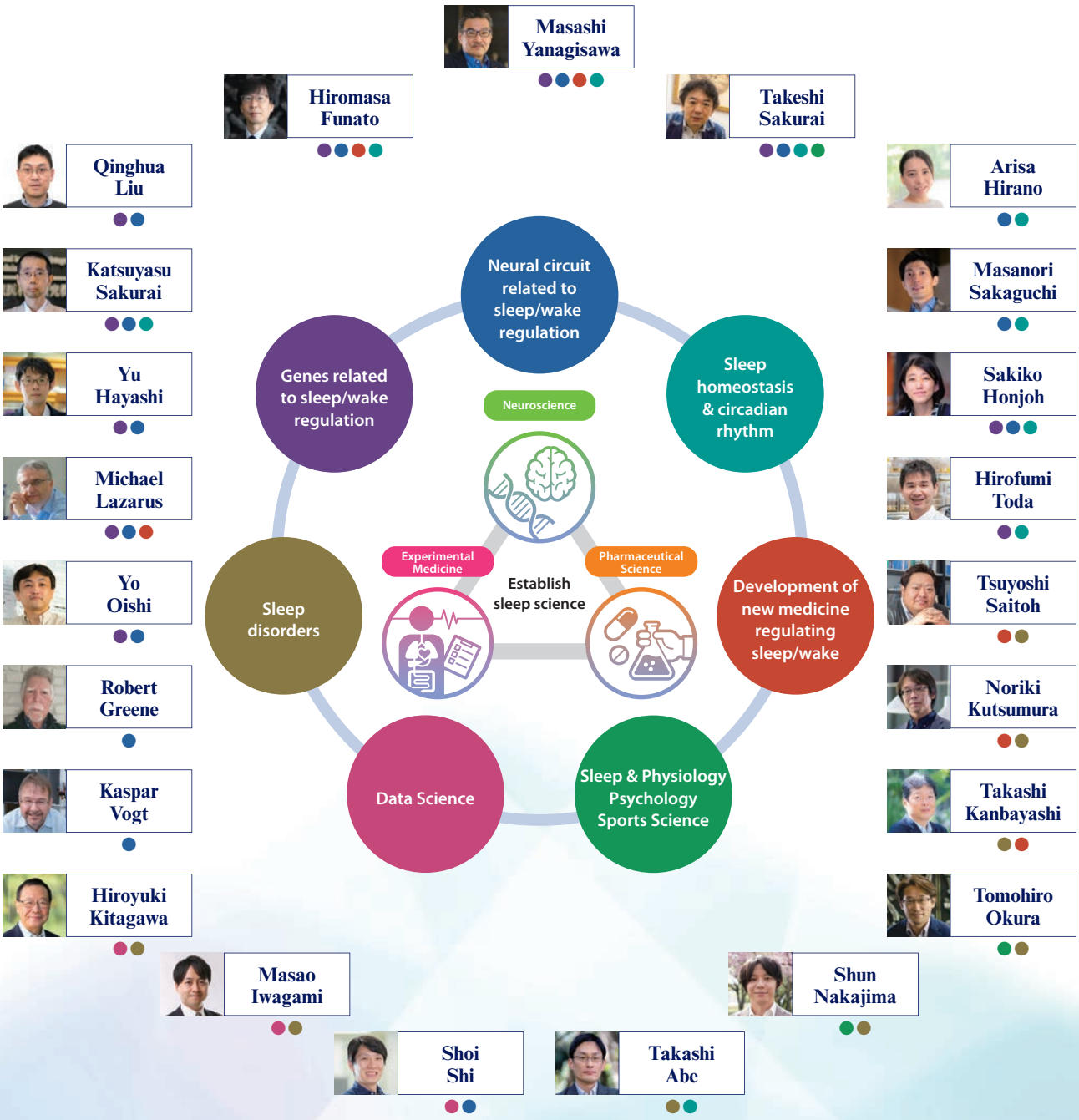
Our missions

mission 1	To elucidate the function of sleep and the fundamental mechanisms of sleep/wake regulation
mission 2	To elucidate molecular pathogenesis of sleep disorders and related diseases
mission 3	To develop preventive measures, diagnostic methods, and treatments for sleep

To accomplish the missions above, IIIS has established a highly ambitious and novel research field, "sleep sciences", by integrating basic neurobiology, experimental medicine and pharmaceutical science.

About Labs

There are seventeen core labs including twenty-three PIs, and fifteen collaborative groups with domestic and overseas labs in IIIS, covering various research fields e.g. molecular genetics, neuroscience, physiology, medicinal chemistry, human sleep physiology, etc. Those labs collaborate with each other to drive forward innovative sleep research.



Satellite

Overseas Satellite Groups

UTSouthwestern Medical Center
HARVARD MEDICAL SCHOOL
NIBS
UNIVERSITY OF OXFORD

Domestic Satellite Labs

Genshiro A. Sunagawa
Masayuki Matsumoto
Morimitsu Kurino
Yuichi Inoue
Hiroyasu Ando

Collaborative Research Group

Hitoshi Shimano
Haruka Ozaki
Akiyoshi Fukamizu
Toshiyuki Amagasa
Satoru Takahashi
Shinji Saiki

Members

Aiming to uncover the reciprocal linkage between intracellular events and sleep/wakeful behavior

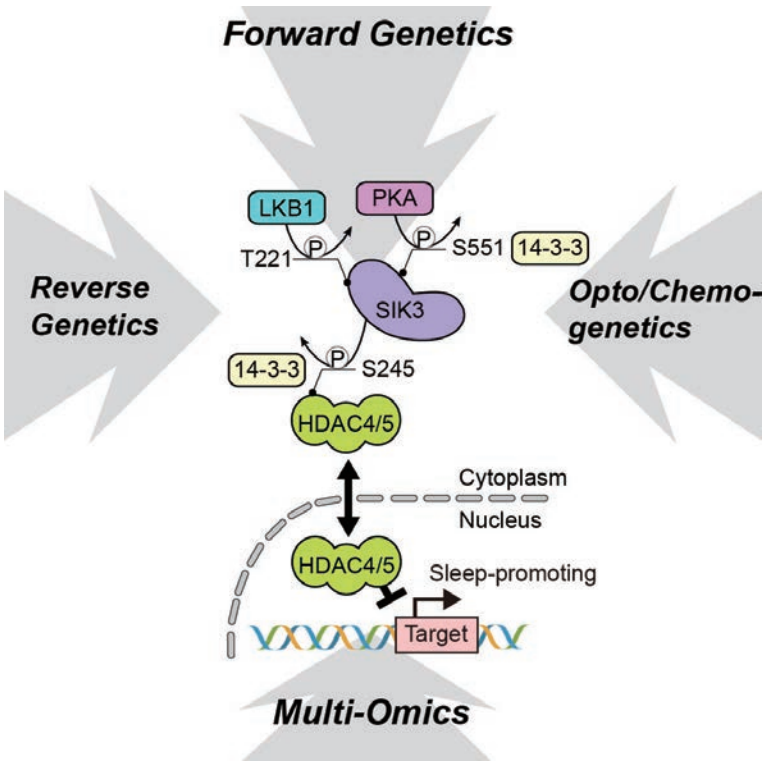
Masashi Yanagisawa
Director

Hiromasa Funato

Our lab has been conducting forward genetic research on sleep/wakefulness using randomly mutagenized mice. Luckily, we succeeded in identifying a protein kinase SIK3, histone deacetylase HDAC4, and a non-selective cation channel NALCN as novel molecules regulating sleep. Further studies using gene-modified mice and AAV-based gene manipulation have revealed that the LKB1-SIK3-HDAC4/5 pathway constitutes intracellular signaling that regulates sleep need. To unravel an enigmatic molecular mechanism for sleep need, we employ a variety of research techniques including multi-omics approaches, such as quantitative phosphoproteomics and single-cell RNA-seq. In addition, the long sleeper phenotype of *Sik3* mutant mice provides us a unique opportunity to examine the benefit of long total sleep time in aging, metabolism, and other phenotypes relevant to human health and diseases.

Nalcn-mutant mice (*Dreamless* mutant mice) show a short total REM sleep and short duration of REM sleep episode. We aim to understand how REM sleep episode is maintained and how total REM sleep time is homeostatically regulated through our research focusing on NALCN.

Importantly, we continue the forward genetic screening to discover novel genes regulating sleep/wakefulness.



Forward genetic studies with other state-of-the-art techniques have identified the LKB1-SIK3-HDAC4/5 pathway regulates the quantity and quality of NREM sleep.

Just enjoy journey of research!
~ There is always something beyond our expect

Takeshi Sakurai
Vice Director

A brain is the device that processes huge amount of information via nerve cells called neurons. How animal's brain interprets information from the external world and trigger appropriate behaviors along with autonomic/neuroendocrine responses? Our group combines optogenetics/pharmacogenetics and cutting-edge genetics in mice to address this question at a high level of precision.

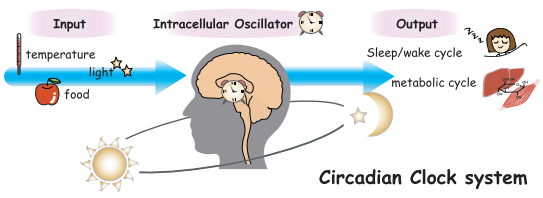
We try to identify substances, neurons and neuronal pathways that are involved in eliciting particular behaviors by means of various histological and physiological techniques applied in genetically-modified mice. We manipulate synaptic transmissions or neuronal excitability in a cell or pathway specific manner to characterize the consequences of those manipulations on the behavior and other physiological responses.

These techniques allow us to study the physiological function of neuronal pathway and substances in the regulatory mechanisms of our behavior. Sleep/wakefulness behavior, emotion, circadian rhythm and social behaviors are our current interest. Along with its academic values, the elucidation of mechanisms of these functions may lead to treatments of various diseases.

We examine function of neuronal pathways and neurotransimitters in the regulation of sleep/wakefulness states and behavior, by means of optogenetics, which enables us to manipulate particular neuronal circuits.

From molecular to behavior: Aiming to understand mysterious biological phenomenon "Sleep" at various levels

We aim to understand why and how we sleep at night and wake up in the morning. In almost organisms living on the earth, many biological processes including sleep exhibit rhythms with a period of ~24 hours, which is called as circadian rhythms. Well-coordinated rhythms by internal time-keeping system, circadian clock, is essential for physical and mental health. We previously identified several gene variants in clock genes altering sleep/wake pattern in humans by forward genetics approach. It is thus well established that the circadian clock has a great impact on sleep/wake rhythms, while the neural pathway from the master clock in the brain (suprachiasmatic nucleus, SCN) to sleep/wake-regulating regions is still elusive. To understand the neural network controlling the circadian sleep behavior, we utilize gene-modified animals, macro injection and opto/chemo-genetics technics to evaluate the effect of manipulation of neurons in the SCN or clock-target regions on sleep/wake rhythms. In addition to the output pathway from the clock, we are also interested in oscillatory mechanism of the clock within the SCN neurons (intracellular oscillator) as well as mechanism of entrainment of the clock to environmental cycle such as light-dark cycle (input pathway), which are considered as three main factors of the circadian clock. We believe that understanding of the whole picture of the circadian clock is key to advance sleep study.



Circadian Clock system

The circadian clocks receive virous stimuli, such as light, temperature and feeding to entrain to the environmental cycles. The basic structure of the circadian clock is an intracellular molecular oscillator composed of several clock genes. The master clock (center clock) resides in the suprachiasmatic nucleus (SCN) in the hypothalamus in mammals. Through neural circuits, various brain regions input time information from SCN to achieve biological rhythms including sleep/wake rhythms, while it has been unknown which circuit is actually involved in the output pathway.

Arisa Hirano

Why do we fall asleep when bored?
~ The gating of sleep by motivated behavior

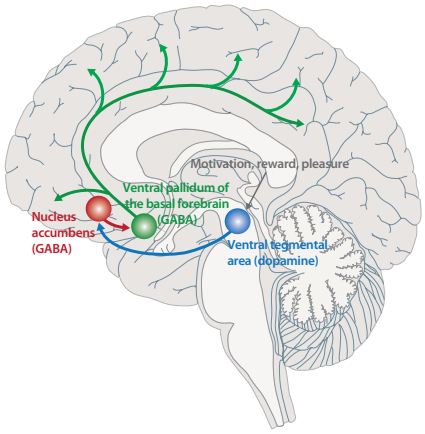
Michael Lazarus

The investigative focus of our laboratory is the cellular and synaptic basis by which the brain regulates sleep and wakefulness. Our experiments seek to link the activity of defined sets of neurons with neurobehavioral and electroencephalographic outcomes in behaving animals by using innovative genetically or chemically engineered systems (optogenetics, chemogenetics or optopharmacology) in conjunction with recording of the electrical activity produced by the brain or in-vivo imaging (fiber-optic endomicroscopy).

For example, we investigate the control of sleep and wakefulness by the mesolimbic pathway comprising the ventral tegmental area and nucleus accumbens. As the mesolimbic pathway is implicated in motivational and cognitive behaviors, changes in vigilant states are likely associated with the motivational and cognitive responses in animals. Moreover, our laboratory is exploring novel agents for the treatment of insomnia by targeting mesolimbic cell populations that have the ability to produce sleep.

We also employ single-cell or spatial gene expression profiling to understand how the sleep/immune system crosstalk is regulated at cellular and molecular levels.

Motivation is a sleep-regulating factor



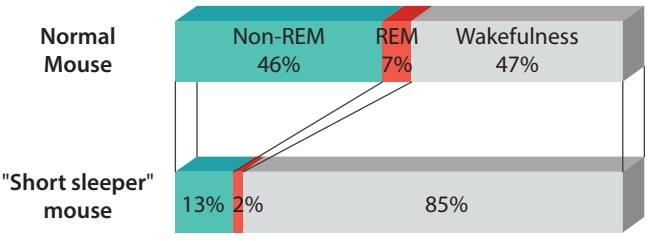
In the absence of motivational stimuli, a tonic sleep drive by the NAc may allow the brain to fall asleep by depressing arousal circuits in the basal forebrain.

To elucidate the mechanism and necessity of sleep with mice like “short sleepers”

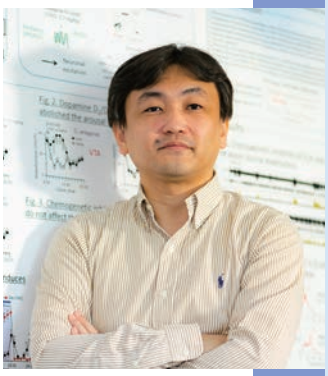
People spend approximately one-third of their life sleeping. Why sleep is compulsory for human life and cannot be avoided, however, remains unclear. It is important to understand why sleep is necessary and how sleep is controlled – not only to elucidate physiologic behavior but also to enhance our quality of life.

Recently, in the course of analyzing sleep-wake regulation by the reward system, we happened to create mice that require an extremely low amount of sleep. Surprisingly, these mice do not show an increase in a sleepiness marker despite of the less sleep amount. In addition, they do not show sleep rebound after sleep deprivation. Therefore, the behavior is very similar to that of so-called “short sleepers” – people that can function for long periods of time on little sleep without exhibiting excessive sleepiness. Using multiple “short sleep” models, including this novel mouse model, we study the neural mechanisms of short sleep to clarify the control mechanisms of sleep. We also study the effect of short sleep on other physiologic functions in the body to understand the necessity of sleep.

In close collaboration with Prof. Lazarus, we use many neurobehavioral and biochemical techniques to perform this research.



Amount of sleep and wakefulness of normal and “short sleeper” mice during 1 day. “Short sleeper” mice exhibit a lower amount of sleep.



Yo Oishi

How are memories organized during sleep? ~ The mystery of sleep and memory

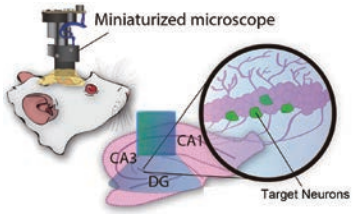
Masanori Sakaguchi

During sleep, a phenomenon called "memory consolidation" occurs, in which we unconsciously organize memories and reinforce necessary memories. There are various states of sleep, such as non-REM sleep and REM sleep, and each of these states plays a different role in memory consolidation. Our research team is challenging to clarify the mechanisms of memory consolidation during sleep and to apply the results to develop a novel therapy for PTSD.

For example, we have developed an AI that analyzes non-REM and REM sleep in real time. We also used a small, light microscope that can be placed on an animal's head to observe the activity of neurons in the brain during sleep. Combining these studies, we are investigating the function of manipulating specific neuronal activity during sleep in memory consolidation.

From these studies, we have found that the activity of newly generated neurons in the adult hippocampus is essential for memory consolidation during sleep. We have also shown that memory consolidation can be manipulated by playing memory-linked sounds during specific phases of sleep. We are conducting clinical research to apply this technology to realize a new home treatment for PTSD patients suffering from traumatic memories.

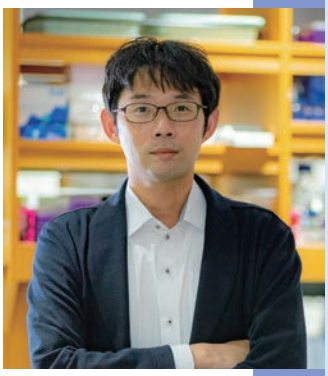
In the future, we hope that these studies will lead to better sleep and the development of new therapies that apply this technology by clarifying the mechanisms of memory processing during sleep.



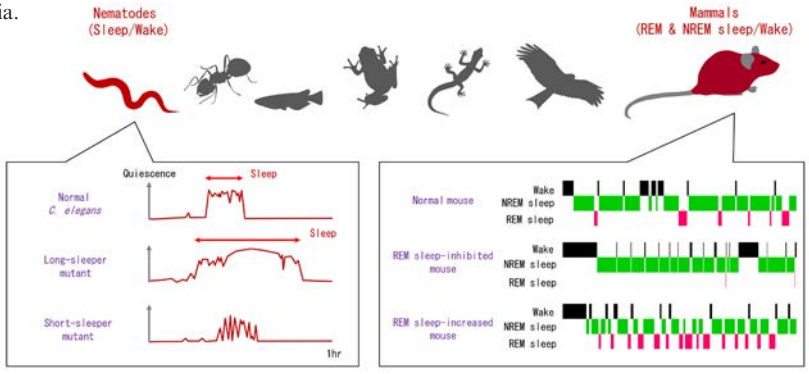
Mini-microscope on the hand and full-scale microscope (behind)

Why we sleep? ~ Addressing the functional roles and evolutionary origin of sleep

Our goal is to elucidate what the function of sleep is. Why sleep is needed to maintain our health still remains largely unknown. To address this large mystery, we focus on two animal species, the roundworm *Caenorhabditis elegans* and mouse. The nervous system of *C. elegans* consists of merely 302 neurons. We previously obtained evidence suggesting that sleep in this simple animal and mammalian sleep are evolutionarily conserved. Furthermore, in mice, we successfully identified neurons that are crucial for the regulation of REM (rapid eye movement) sleep, a major source of vivid dreams, and established mice where REM sleep could be efficiently inhibited. Using these two model animals, we aim to elucidate the roles of sleep at multiple levels from molecular and cellular to individual levels. Moreover, we aim to apply the obtained knowledge to understand and develop treatments for neurological disorders such as dementia.



Yu Hayashi



What does the cortex do during slow wave sleep? ~ To elucidate its mechanisms and functions

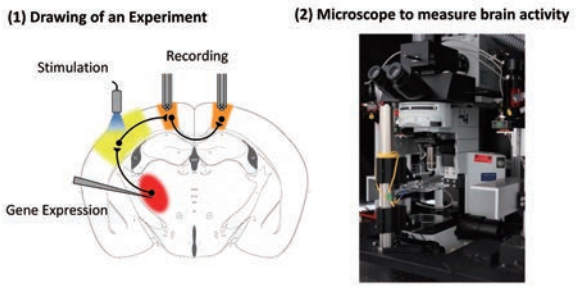
Robert Greene

Kaspar Vogt

We are interested in cortical activity during deep, so-called non-REM or slow wave sleep, and during waking. Slow wave sleep restores brain function from the reduced state after long waking to the refreshed state after waking up. It also improves memory and has many other beneficial effects. How slow wave sleep does this things is currently not known.

The cortex is the outermost part of the brain; higher functions such as perception, consciousness and learning and memory depend on it. We record electrical signals from individual neurons or groups of them in freely behaving mice and also use in-vivo imaging to study the activity of these neurons. In slow wave sleep cortical neurons show distinct rhythmic activity, different from waking. The more an animal needs to sleep, the stronger this rhythm becomes.

We want to understand what controls and creates this rhythm and how it changes the ways in which neurons interact. For this we develop new algorithms to analyze the activity of neurons and use molecular tools to activate or silence certain types of neurons with high precision.



(1) Schematic of a brain with the postiton of the light stimulus and the electrodes that record the response. With this experiment we can stimulate the brain in all states waking and sleeping and can measure the response. We have found that the responses are larger in sleep than in waking.
(2) With this microscope we can look into the brain of a living mouse. We examine special mice, which express a protein in their brain that changes its visibility, depending on how active the nerve cells in the brain are. We want to understand how the activity in a sleeping brain differs from waking.

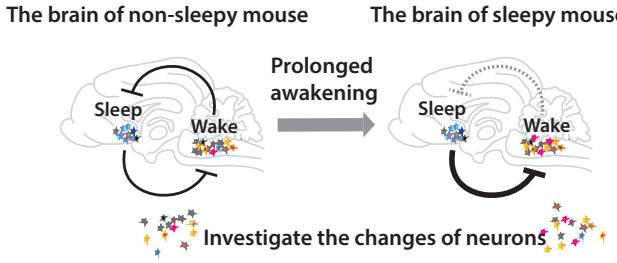
How to generate mice who never sleep? ~ To fully understand and regulate sleep

We are interested in homeostatic sleep/wake regulation in behavioral vigilance states (e.g., mice sleep longer after when they stayed awake longer) and in cortical neural activity (e.g., a cortical region sleeps deeper when the region has been active during prior waking).

It is becoming clearer that brain regions contribute to sleep/wake regulation to a different extent. Several wake, and nonREM sleep and REM (REM; rapid eye movement) sleep-promoting or -inhibiting areas have been identified. To understand the nature of the homeostatic regulation, using mice, we investigate what kind of changes the critical sleep/wake regulating centers undergo during persistent waking and subsequent sleep.

As for the cortical activity, we focus on slow wave, a hallmark of NREM sleep EEG. Though it is the best marker for sleep need so far and it plays important roles in sleep-dependent memory consolidation, the underlying neural circuits remain largely unknown. Currently we investigate the role of thalamic matrix cells in slow wave generation.

Sakiko Honjoh



Elucidating the Neural Mechanisms involved in Sleep drive and Appetite

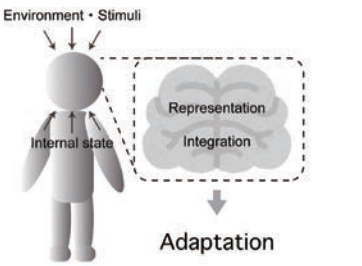
Qinghua Liu

Katsuyasu Sakurai

Living organisms, including humans, survive by adapting to ever-changing internal conditions (physical, physiological, mental, etc.), environment, and stimuli. For example, instinctive behaviors such as appetite and sleep drive are greatly influenced by the internal state of mind, body, and environment. Their disruption can have a profoundly negative impact on healthy daily and social life. Therefore, a comprehensive understanding of the neural mechanisms involved in appetite and desire for sleep is crucial for both individuals and society.

Detailed studies have been conducted on the neural mechanisms of appetite, from the molecular to the neural circuit level. On the other hand, the neural mechanisms of anorexia, a state of decreased appetite, remain largely unknown. Therefore, our research aims to comprehensively understand the neural mechanisms of anorexia from the molecular level to the neural circuit level. To understand the neural circuits, we are focusing on brain regions that monitor brain-organ connections and the state of the body and mind.

Concerning sleep research, we are focusing on the effects of food on sleep. One of these studies seeks to elucidate the neural mechanisms of postprandial sleepiness. Although we frequently experience postprandial sleepiness, its mechanism has not been clarified. We are trying to elucidate the brain-organ coupled signaling mechanisms involved in postprandial sleepiness from the molecular to the neural circuit.



The internal state of mind, body, and environment greatly influences instinctive behaviors such as appetite and sleep drive.

How is the sleepiness represented inside a brain? ~ The power of using fruit flies in sleep research

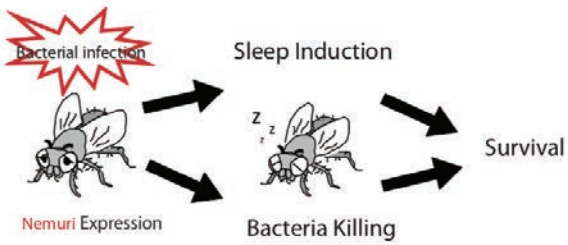
Hirofumi Toda

The main goal of our lab is to understand the molecular and cellular mechanisms of sleep. Sleep is important and conserved in all animals from humans to insects. Yet, the function of sleep: why we need it, and the mechanisms of sleep: how it occurs remains largely mystery.

In order to understand the mechanisms of sleep, we use fruit flies as a model system to tackle such questions because flies are fantastic genetic model organisms especially amenable for genetic screening.

For example, to identify molecular factors that induces sleep, we carried out a genomewide behavioral screen, evaluating over 12,000 fly lines, and found a novel sleep inducing factor named "*nemuri*". Nemuri functions as an anti-microbial peptide that is essential for bacterial infection-induced sleep, suggesting Nemuri served as a key link between sleep and immunity.

Our group combines genetic, biochemical, behavioral and imaging techniques to elucidate the mechanisms of how Nemuri functions inside neurons to induce sleep. Moreover, we aim to identify the mammalian homologue of *nemuri* through behavioral screening by expressing human candidate genes in fly brain. These studies will improve our understanding of how the sleepiness is represented inside the brain.

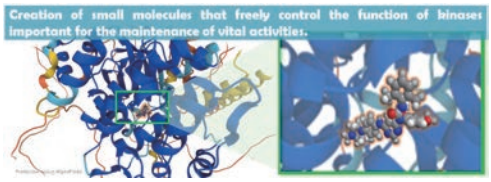


Solving mysteries of life through organic chemistry

Noriki Kutsumura

We are engaged in drug discovery research and drug discovery-related research activities. Medicinal chemistry is very challenging research that is based on many disciplines, including medical science, pharmacology, biochemistry, molecular biology, pharmacology, pharmacokinetics, and drug formulation, with a focus on synthetic organic chemistry. Due to the nature of the discipline, it may be said that one of the characteristics of medicinal chemistry research is that it often develops into collaborative research with companies and other universities.

Our main research activities can be broadly categorized into "chemical synthesis of small molecule compounds that act *in vivo*" and "development of chemical reactions useful for synthesizing such biologically active molecules". In the synthesis of small molecules acting *in vivo*, we aim to create "superior molecules" through structure-activity relationship study and structure optimization study. Research themes, for example, include the synthesis of compounds that specifically act on protein phosphatases and structure-activity relationship studies based on natural products acting on orexin receptors, both of which lead to the elucidation of sleep/wake mechanisms. On the other hand, in the development of chemical reactions, we aim to develop novel chemical reagents and/or synthetic methods that anyone can easily utilize. Specifically, we are interested in the development of sulfurizing reagents without bad odor or chemoselective halogenation methods. Our goal is to develop innovative chemical reactions that can be used by pharmaceutical and chemical companies in near future.



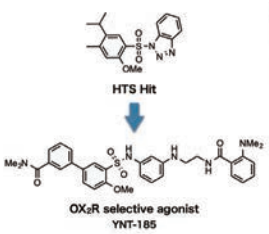
Innovative new drugs from IIIS

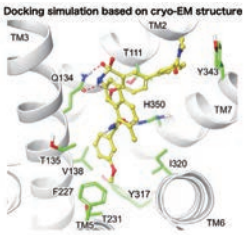
Our group is the only chemistry-based group in IIIS engaged in drug discovery research with the goal of 'New Drugs from IIIS!'.

Our group focuses on a class of membrane proteins called G-protein coupled receptors (GPCRs). GPCRs are the largest protein family in the human genome and are involved in a wide variety of diseases. Therefore, approximately 30% of all market drugs target GPCRs, making them the biggest group of drug targets. Our group is mainly targeting orexin receptors involved in arousal and emotion, opioid receptors involved in pain and itch, and adenosine receptors involved in sleep and inflammation to serve new drugs for sleep disorders such as narcolepsy and insomnia, pain, drug dependence, depression, anxiety, and other psychiatric disorders. For example, in 2015, we discovered the first orexin 2 receptor (OX2R) selective agonist, YNT-185, from Hit compounds obtained through a high-throughput screening (HTS) campaign and demonstrated that OX2R agonists are effective for the treatment of narcolepsy.

Recently, we have been challenging the Structure-Based Drug Design (SBDD) of GPCR-targeting drugs by incorporating the latest technologies such as cryo-EM SPA and wide-range signal analysis toward the logical design of drugs without side effects.

We have also been developing innovative chemical tools that contribute to biology and medical science by combining our drugs and chemical reactions with the latest biological techniques.





Tsuyoshi Saitoh

Understanding the human mind and behavior related to sleep

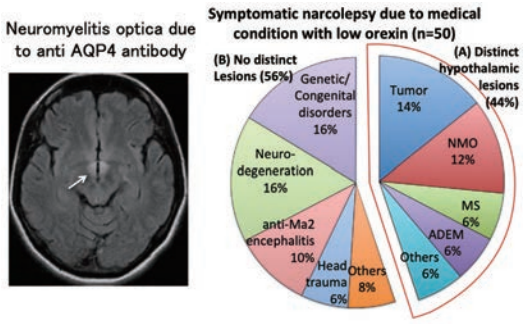
Takashi Abe

Our laboratory aims to understand human mind and behavior related to sleep. Currently, we are focusing on two main areas of research. (1) Our laboratory is conducting research to understand the role of human REM sleep in waking emotional processing. We have discovered a brain potential that occurs before rapid eye movements during REM sleep, which we have named the pre-rapid-eye-movement negativity (PRN). Our research also found that the PRN originates from the ventromedial prefrontal cortex. This brain region is involved in emotional regulation, so we believe that the PRN reflects emotional processes during REM sleep. We are using the PRN as a marker to investigate the psychological functions of REM sleep. (2) Our laboratory is conducting research to understand and mitigate performance deficits caused by sleep loss in order to prevent accidents and human errors related to sleep loss. One aspect of this research involves developing a new system for evaluating and predicting declines in vigilant attention due to sleep loss using an accurate and unobtrusive measure. We have identified several new markers for vigilant attention and developed a new algorithm for detecting the level of vigilant attention by integrating these markers. We are conducting research towards its practical implementation. In addition, we are also exploring ways to prevent performance deficits caused by sleep loss. Our laboratory is developing non-invasive methods for promoting sleep. Through these research and technological developments, we aim to prevent accidents and human errors related to sleep loss.

Using a laboratory that can simultaneously measure the sleep and wakefulness of four people, we are conducting research how sleep and sleepiness relate to the human mind and behavior.

Elucidating the pathogenesis of central hypersomnia and schizophrenia through research on neural autoantibodies

It has already been 20 years since orexin was discovered, but it is still the only biochemical marker for diagnosis of sleep wake disorders. Other than orexin, diagnosis is made only by sleep polygraph examinations and clinical symptoms. Since orexin is decreased in narcolepsy, it has been measured from 2000 for a definitive diagnosis for narcolepsy and about 3000 samples have been measured. Orexin is also an important biomarker of symptomatic hypersomnia due to hypothalamic lesions. We have reported symptomatic narcolepsy due to AQP4 antibody as the first sleep wake disorder involving an autoimmune mechanism. In addition to cases with hypothalamic lesion, it has been reported that orexin decreases and symptomatic narcolepsy occurs in hereditary diseases and neurodegenerative diseases. One of the goals of our group is to clarify the pathophysiology of hypersomnia through the study of symptomatic narcolepsy.



Left: An MRI image of NMO with hypersomnia. Hypothalamus and orexin system are impaired by AQP4 antibody. Right: The classification symptomatic narcolepsy with decreased orexin levels. NMO, MS, ADEM, Ma2 encephalitis are caused due to the autoimmune mechanism.

Similar to AQP4 antibody, NMDA receptor antibody that acts on the surface of cell membranes causes NMDA receptor encephal it is with psychosis. Schizophrenia is a disease of unknown cause, but we believe that it may also develop due to an autoimmune mechanism, such as NMDA receptor antibody. We are continuing to consider this direction of research.

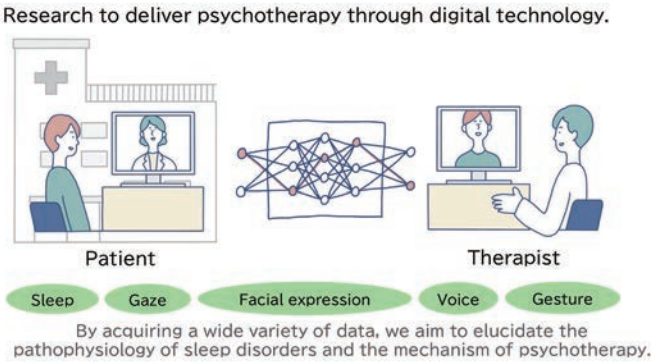
Takashi Kanbayashi

Supporting people's lives through psychotherapy and digital technology

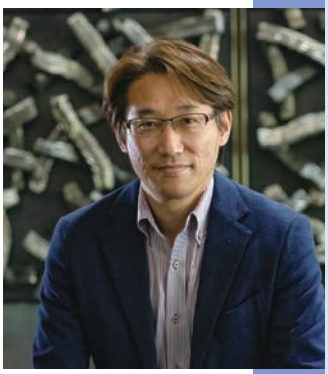
Shun Nakajima

Globally, one in seven individuals experiences sleep problems. While pharmacological therapy might be the common perception for those with insomnia, cognitive-behavioral therapy (CBT-I), a form of psychotherapy, is advocated as the first-choice treatment for insomnia. However, there remains a lack of widespread access to cognitive-behavioral therapy for insomnia (CBT-I). In response to this issue, our research laboratory is conducting studies to provide effective psychotherapy to individuals of all ages who are suffering from sleep and mental health problems.

Furthermore, we have recently initiated research on digitizing therapists' empathic abilities and implementing empathy into AI therapists. Additionally, we are developing psychotherapy based on objective markers derived from various digital devices. We believe that advancing research that combines subjective and objective data could lead to breakthroughs in sleep healthcare.



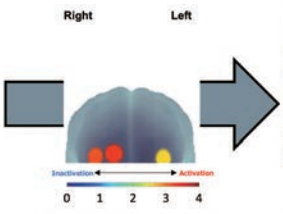
Exploring safe and enjoyable exercise conditions to improve sleep



Tomohiro Okura

Methods of improving sleep are divided into drug therapy and non-pharmacological therapy. Because various side effects have been reported in the elderly, American Geriatrics Society recommends that sleeping pills not be prescribed. We have focused on the study regarding exercise therapy for good sleep. Few previous studies examine the effects of exercise on sleep in the elderly, and it is unknown what kind of exercise may be effective in improving sleep. Also, most of the previous studies examined on simple exercise by using a treadmill or cycling ergometer. In order to improve sleep by exercise, it is important to continue doing exercise, but the aforementioned exercise is easy to get tired of and has a high risk of injury. So, we put safe and enjoyable exercise first and comprehensively reviewed the intensity, type, implementation time, and form of exercise. As a result, we confirmed that performing low-intensity aerobic exercise for 30 minutes at night is effective for improving sleep. In addition, compared to simple exercise multi-tasking exercise with stimulating frontal lobe showed the effect of increasing deep sleep along with activation of the frontal lobe immediately after exercise. In other words, appropriately stimulating frontal lobe and going to bed may be effective in improving sleep for the elderly.

Enjoyable exercise



Activation of the frontal lobe

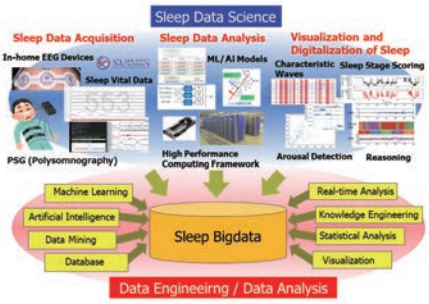
Increasing deep sleep

Sleep data science and engineering ~ Big data analysis, databases, data mining

Hiroyuki Kitagawa

Data exploration is recognized as the fourth paradigm of science after experimentation, theory, and simulation. Data-intensive research has been more and more important in science, and sleep medicine is no exception. In the past, special measuring equipment and hospitalization were required to collect sleep data for analysis and diagnosis. Advances in IT have made it possible to easily measure sleep data at home. We are approaching the science of sleep from a data science and engineering perspective.

One of our recent research topics is automatic sleep stage scoring. Sleep is classified into stages such as REM sleep, non-REM sleep, and wake, and the analysis of stage transitions is essential in understanding sleep. Conventionally, sleep stages were determined by experts, but this requires a high level of expertise and a lot of time. By utilizing machine learning technology such as deep learning, we have developed a system that can automatically determine sleep stages with the same accuracy as experts and can present the basis for the determination. Other research themes include improving the robustness of analysis against noise, technology to flexibly respond to the characteristics of each subject, and real-time analysis of electroencephalogram data acquired during sleep.



To strengthen our backbone technologies, we are also actively engaged in research on innovative technologies in data engineering and data analysis such as big data analysis, databases, data mining, and machine learning in collaboration with the Center for Computational Sciences.

Establishing “Sleep epidemiology” as a branch of epidemiology

Masao Iwagami

Epidemiology is the study of diseases in populations and its scope ranges from disease causation and prevalence to disease prevention. Environmental epidemiology, nutritional epidemiology, genetic epidemiology, among others, have been established as the main subfields of epidemiology. Although epidemiological research on sleep has been conducted as part of various cohort studies, “sleep epidemiology” is not yet a fully established branch of epidemiology. This is mainly due to the difficulty of measuring sleep objectively.

However, recent advances in technology enable at-home monitoring of brain waves during sleep and recording of sleep parameters using smartphones. The opportunity for the development of sleep epidemiology arises when large-scale data acquisition becomes possible. Our goal is to collect objective sleep data on a large scale, analyze it in conjunction with various health information, clarify the true relationship between sleep and disease, and extend people's healthy life expectancy through improved sleep.

InSomnograf, a device to measure brain waves during sleep at home (S'UIMIN Inc., a start-up company from the University of Tsukuba)

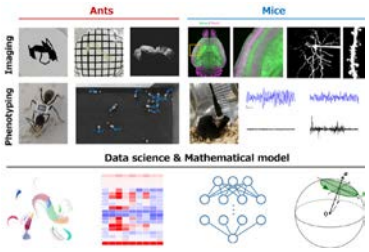
Furthermore, routinely collected clinical data have recently been accumulated and made available for clinical research in Japan as well, including records of consultation and prescriptions for narcolepsy, sleep apnea syndrome, and insomnia. We will also contribute to the establishment of sleep epidemiology by promoting epidemiological research on sleep-related diseases utilizing these records.

Exploring the Conservation and Diversity of Sleep by Comparative Neuroscience

Shoi Shi

Comparative neuroscience has a long tradition of studying the structure and function of the central nervous system. Advances in imaging technologies have enabled the examination of structural and functional properties at the single-spine level in some model organisms. However, it is undeniable that neural structures in a given species are constrained by the unique evolutionary history and characteristics of that species. As such, we propose a new approach, referred to as Comparative Neuroscience 2.0, in which model and non-model organisms are compared at the same resolution to distinguish species-specific features from those that are evolutionarily conserved. This approach allows for the identification of the smallest structural and functional units that are shared across organisms.

Sleep is a physiologic process that is conserved across a diverse array of organisms, including mammals, birds, and reptiles. Our research group aims to understand the mechanisms and functions of sleep, as well as its evolutionary significance. To this end, we study mice as a representative vertebrate and ants as a representative arthropod. We also collaborate with researchers studying other non-model animals and developing new technologies for comparative neuroscience. Our team comprises members with diverse expertise, including neurosciences, genetics, computational science, and other fields, and we employ a range of techniques to realize quantitative comparisons between species.



We are creating novel imaging and phenotyping techniques specifically designed for non-model organisms. By integrating these technologies with data science and mathematical techniques including clustering, machine learning, and mathematical modeling, we are able to investigate and expand the field of comparative neuroscience.

Satellite and University of Tsukuba Collaborative Research Group

Our sleep research network is also spreading outside of IIIS. Through collaboration with fifteen satellite laboratories and collaborative groups in University of Tsukuba, we are powerfully pushing ahead with unique sleep research including basic and translational research.

Satellite

Overseas Satellite Groups

UT Southwestern Medical Center

THE HARVARD MEDICAL SCHOOL

NIBS

UNIVERSITY OF OXFORD

Domestic Satellite Labs

Genshiro A. Sunagawa
Center for Biosystems Dynamics Research, RIKEN

Morimitsu Kurino
Faculty of Economics, Keio University

Hiroyasu Ando
Advanced Institute for Materials Research, Tohoku University

Masayuki Matsumoto
Center for the Evolutionary Origins of Human Behavior, Kyoto University

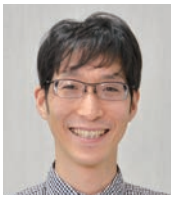
Yuichi Inoue
Institute of Neuropsychiatry

Collaborative Research Group

Hitoshi Shimano
Faculty of Medicine

Akiyoshi Fukamizu
Faulty of Life and Environmental Sciences

Satoru Takahashi
Faculty of Medicine



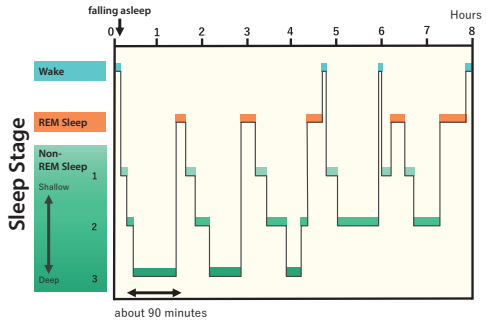
Haruka Ozaki
Faculty of Medicine

Toshiyuki Amagasa
Center for Computational Sciences

Shinji Saiki
Faculty of Medicine

Glossary

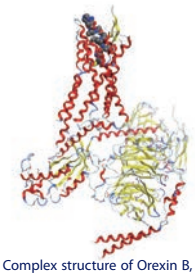
Non-REM Sleep/REM Sleep
(REM; Rapid Eye Movement)



Our sleep can be classified into two stages by brain wave, non-REM sleep and REM sleep. Just after falling asleep, a shallow non-REM sleep begins and it gradually becomes deeper as time passes. As brain activity decreases compared with that during arousal, non-REM sleep is often considered as "sleep of the brain". Additionally, during deep non-REM sleep, a characteristic brain wave called “slow wave” is observed. This is caused by the synchronization of neuronal activity in the brain. After about 90 minutes of non-REM sleep, REM sleep occurs. During REM sleep, skeletal muscles relax while the brain activity increases, and vivid dreams are typically experienced. Although it is often mentioned that non-REM sleep is a deep sleep and that REM sleep is a shallow sleep, this is not really correct. These two sleep stages are completely different. In overnight sleep, we regularly repeat the periodic of non-REM sleep and REM sleep cycles, then eventually leading to wakefulness.

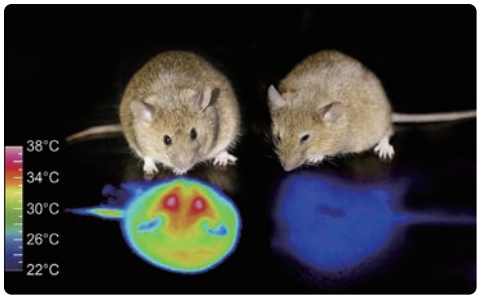
Orexin

Orexin is a substance in the brain (neuropeptide) that regulates sleep and arousal, discovered in 1998 by Dr. Masashi Yanagisawa and Dr. Takeshi Sakurai. It is secreted from neurons in the hypothalamus and functions to keep the arousal state. It is known that orexin deficiency causes narcolepsy, patients of which experience excessive daytime sleepiness, uncontrollable sleep attacks, and sudden loss of muscle tone triggered by intense emotions such as surprise and amusement.
Orexin interacts with proteins called “receptors” on the surface of neurons. There are two types of orexin receptors, OX1R and OX2R, and these receptors are also research and development targets for pharmaceuticals. "Antagonists", which compete with orexin to bind to receptors and inhibit its effect, have been used in medicines such as Suvorexant, Lemborexant, and Daridorexant for the treatment of insomnia. Conversely, "Agonists", which bind to the orexin receptors and cause the same effect as orexin are expected to be applied to treatment for narcolepsy. Several compounds have been found already, and some clinical studies have been conducted to confirm their effectiveness and safety.



Complex structure of Orexin B, OX2R, and G proteins

Q-neuron-induced hypothermia and hypometabolism (QIH)



Normal mouse (left, body temperature 37°C) and QIH mouse (right, body temperature 23°C). QIH mouse

QIH is an artificially induced hypothermic and hypometabolic state in mice or rat, which has similar characteristics to hibernation observed in some kinds of species, such as Syrian hamsters and ground squirrels. In 2020, Dr. Takeshi Sakurai, the vice director of IIIS, discovered that quiescence-inducing neurons (Q neurons) in a small population in the hypothalamus potentially induce this hibernation-like state, QIH. An excitation of Q neurons by chemogenetics or optogenetics rapidly decreases mouse body temperature, while the homeostatic regulation of the body temperature is still conserved. Oxygen consumption, heart rate, locomotor activity and brain activity are also largely suppressed during the excitation of Q neurons. However, once the neuronal manipulation stops, these parameters including the body temperature return to normal levels without any damages in the tissues. This artificial hibernation technique has many potentials in clinical application. For example, in the emergency medical care or tissue transplantation, we are possibly able to prevent server tissue damages by reducing the oxygen demand, leading to an increase of the survival rate. Future applications could include manned space exploration.

Forward Genetics

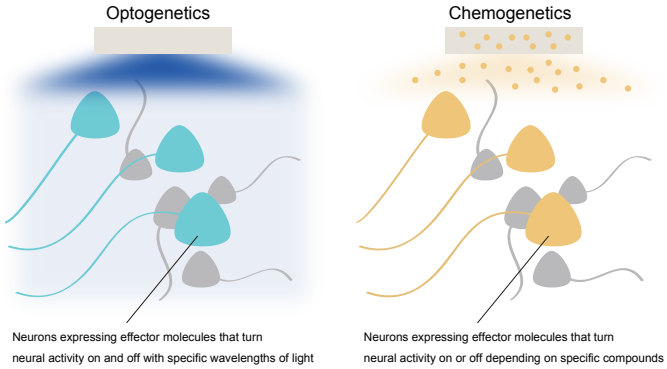
Forward Genetics is a research approach for exploring the genetic basis responsible for a certain inherited characteristic (phenotype). For example, IIIS researchers are searching for novel genes involved in sleep/arousal regulation as follows.

1. Using a certain chemical, generate enormous numbers of animals that have random mutations in their genome. (Usually, animals with short generation time such as nematodes and Drosophila are used, but at IIIS, forward genetics research is being conducted using mice, which is unprecedented in the world.)
2. Observe the brain waves of the offspring of mice obtained above to find mice with sleep abnormalities. Then, we examine whether the abnormality is inherited by the next generation.
3. Analyze the genome of those mutants and find out gene mutations responsible for inherited sleep abnormalities.

Although examining the brain waves of a very large number of mice is time-consuming and labor-intensive, this hypothesis-free approach may lead us to serendipitous discoveries of sleep-regulating genes and molecular mechanisms of sleep regulation.

The sleep measurement facility for mice in IIIS. For forward genetics research, a large-scale facility is necessary.

Optogenetics • Chemogenetics



Neurons, the cells that make up the brain, use electrical signals to process and transmit information. Changes in the electrical potential between the outside and inside neurons generate these electrical signals. Therefore, neural activity can be turned on or off if we can artificially cause a change in the potential between the inside and outside of a neuron.

Techniques that can artificially alter neural activity include optogenetics and chemogenetics. Both techniques require that the neurons whose neural activity is manipulated express effector molecules, using genetic engineering, to cause a change in the cell's potential. Optogenetics and chemogenetics can artificially alter neural activity by activating effector molecules through irradiating specific wavelengths of light and introducing specific compounds, respectively.

Proteomics

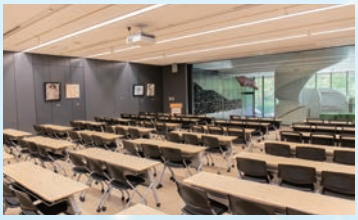
Proteomics is the method to comprehensively identify the proteins in cells or tissues and elucidate their functions using a mass spectrometer. All biological phenomena are driven by various proteins encoded in the genome. "Post-translational modifications" is one of the important processes to regulate the functions of various proteins. “Phosphorylation”, one of the post-translational modifications, switches the activity of proteins by adding a phosphate group to the proteins. The phosphoproteomic analysis enables us to comprehensively reveal the phosphorylation status of all proteins.

While the genomic information in all cells is basically the same, the information on proteins varies among the cell types or tissue types, and changes over time or depending on the environment, even in the same animal. Proteomic and phosphoproteomic analyses allow researchers to obtain more detailed and complex information about the molecular mechanisms of biological phenomena.

Mass spectrometer for proteomics

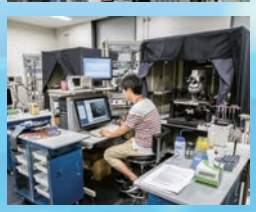




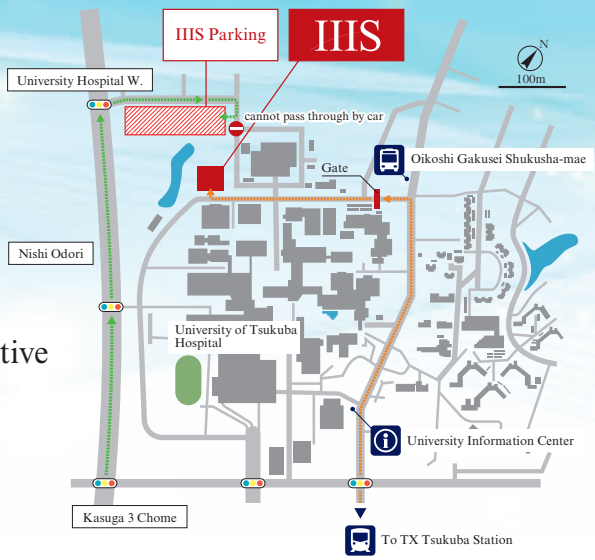






IIIS
INTERNATIONAL INSTITUTE FOR INTEGRATIVE SLEEP MEDICINE

International Institute for Integrative Sleep Medicine
University of Tsukuba
1-1-1 Tennodai, Tsukuba, Ibaraki, 〒305-8575
TEL/FAX +81-29-853-5857 / 3782

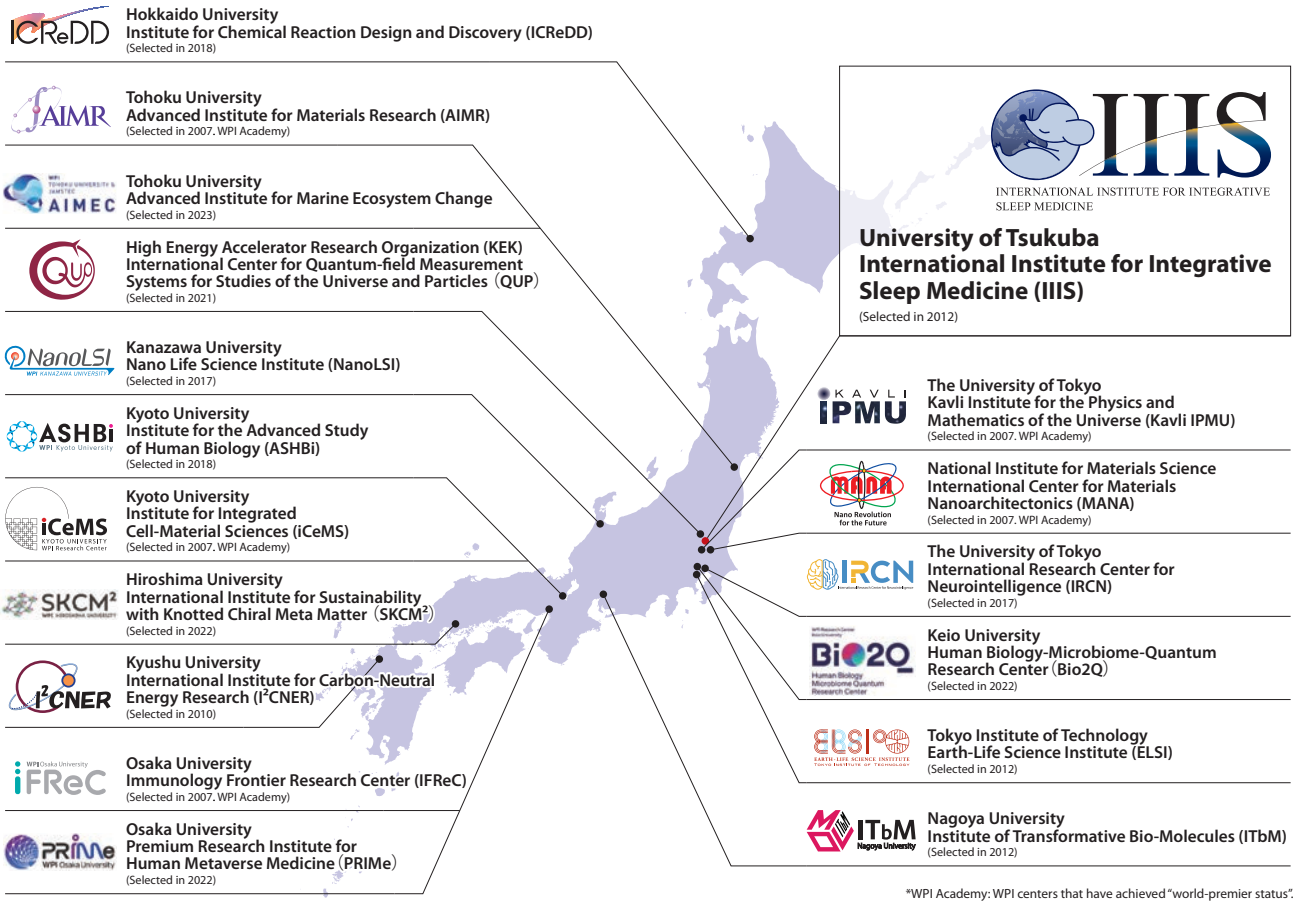


About WPI

The World Premier International Research Center Initiative (WPI) was launched in 2007 by the Japanese Government's Ministry of Education, Culture, Sports, Science and Technology (MEXT) with the aim of building globally visible research centers with high research standards and excellent research environments to accommodate globally prominent researchers. The International Institute for Integrative Sleep Medicine (WPI-IIIS) was established on December 1, 2012, following the FY 2012 selection round of its application for the WPI. The initiative seeks to create a vibrant environment where frontline researchers, regardless of nationality, are invited from around the world to engage in research where they are accompanied by an administrative support system that allows these scientists to fully devote themselves to their research.

Four Missions of WPI

1. Advancing leading edge research
2. Establishing international research environments
3. Reforming research organizations
4. Creating interdisciplinary domains



Hokkaido University
Institute for Chemical Reaction Design and Discovery (ICReDD)
(Selected in 2018)

Tohoku University
Advanced Institute for Materials Research (AIMR)
(Selected in 2007. WPI Academy)

Tohoku University
Advanced Institute for Marine Ecosystem Change
(Selected in 2023)

High Energy Accelerator Research Organization (KEK)
International Center for Quantum-field Measurement Systems for Studies of the Universe and Particles (QUP)
(Selected in 2021)

Kanazawa University
Nano Life Science Institute (NanoLSI)
(Selected in 2017)

Kyoto University
Institute for the Advanced Study of Human Biology (ASHBi)
(Selected in 2018)

Kyoto University
Institute for Integrated Cell-Material Sciences (iCeMS)
(Selected in 2007. WPI Academy)

Hiroshima University
International Institute for Sustainability with Knotted Chiral Meta Matter (SKCM²)
(Selected in 2022)

Kyushu University
International Institute for Carbon-Neutral Energy Research (I²CNER)
(Selected in 2010)

Osaka University
Immunology Frontier Research Center (IFReC)
(Selected in 2007. WPI Academy)

Osaka University
Premium Research Institute for Human Metaverse Medicine (PRIMe)
(Selected in 2022)

University of Tsukuba
International Institute for Integrative Sleep Medicine (IIIS)
(Selected in 2012)

The University of Tokyo
Kavli Institute for the Physics and Mathematics of the Universe (Kavli IPMU)
(Selected in 2007. WPI Academy)

National Institute for Materials Science
International Center for Materials Nanoarchitectonics (MANA)
(Selected in 2007. WPI Academy)

The University of Tokyo
International Research Center for Neurointelligence (IRCN)
(Selected in 2017)

Keio University
Human Biology-Microbiome-Quantum Research Center (Bio2Q)
(Selected in 2022)

Tokyo Institute of Technology
Earth-Life Science Institute (ELSI)
(Selected in 2012)

Nagoya University
Institute of Transformative Bio-Molecules (ITbM)
(Selected in 2012)

*WPI Academy: WPI centers that have achieved "world-premier status".

Website


IIIS
NIPPON