

MS7 Kickoff Symposium



Deciphering and Engineering Sleep and Hibernation ~ The Future of Medical Care ~

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Program Manager / Professor
Masashi Yanagisawa

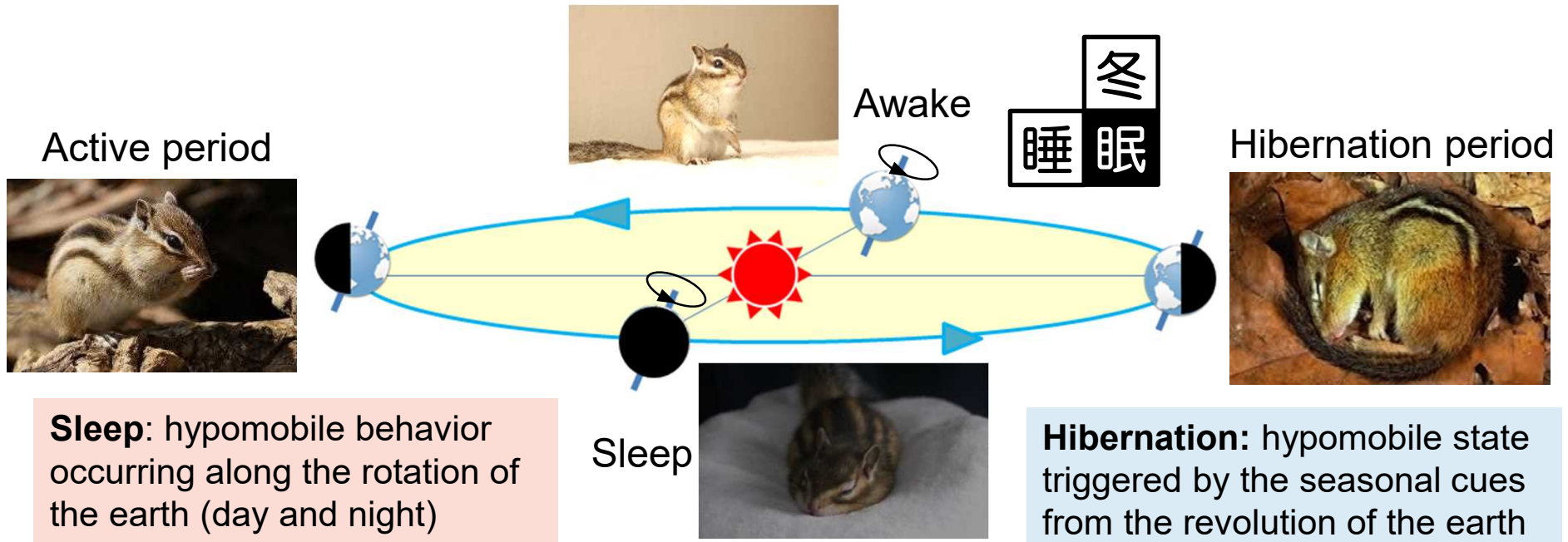
June 26, 2021

International Institute for Integrative Sleep Medicine
University of Tsukuba



Project Goals in 2040 (1):

Sleep and Hibernation: Most challenging mysteries in neuroscience



Sleep duration varies by species

Species	Average Sleeping Time	Species	Average Sleeping Time
Tiger	15.8	Sheep	3.8
Cat	12.1	Elephant	3.3
Chimpanzee	9.7	Horse	2.9
Human	8.0	Giraffe	1.9

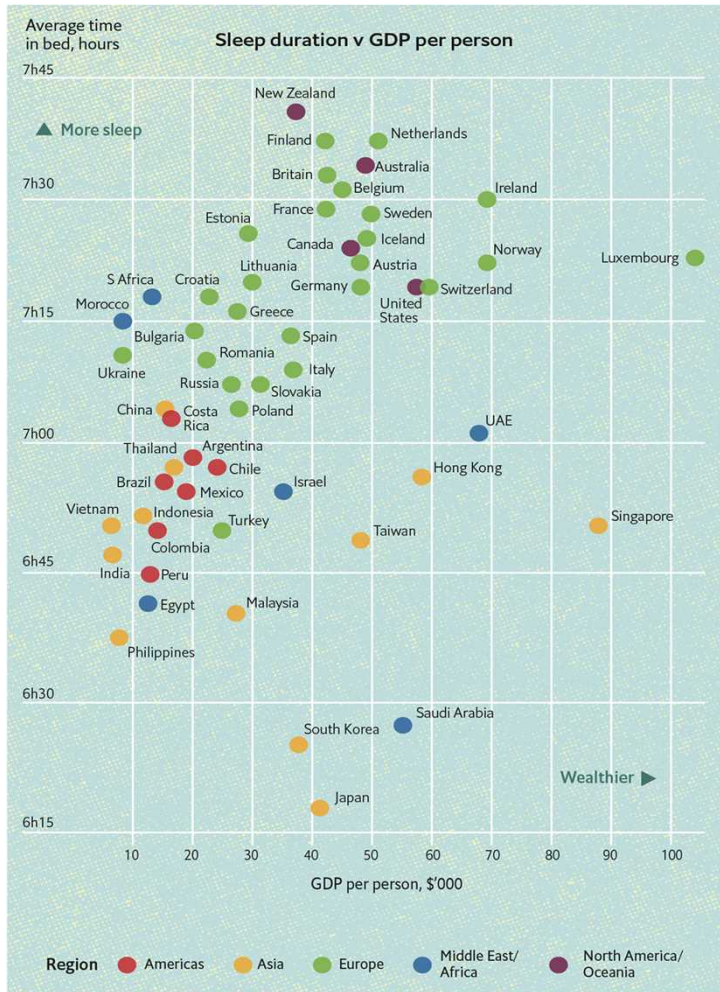
183 species in 7 orders hibernate, out of the 4,070 mammalian species

Order	Family	Number	Typical species
Primate	Cheirogaleidae	3	Fat-tailed dwarf
Carnivores	Bear family	4	Asiatic black bear, Polar bear (female only)
Rodents	Squirrel family	58	Thirteen-lined squirrel

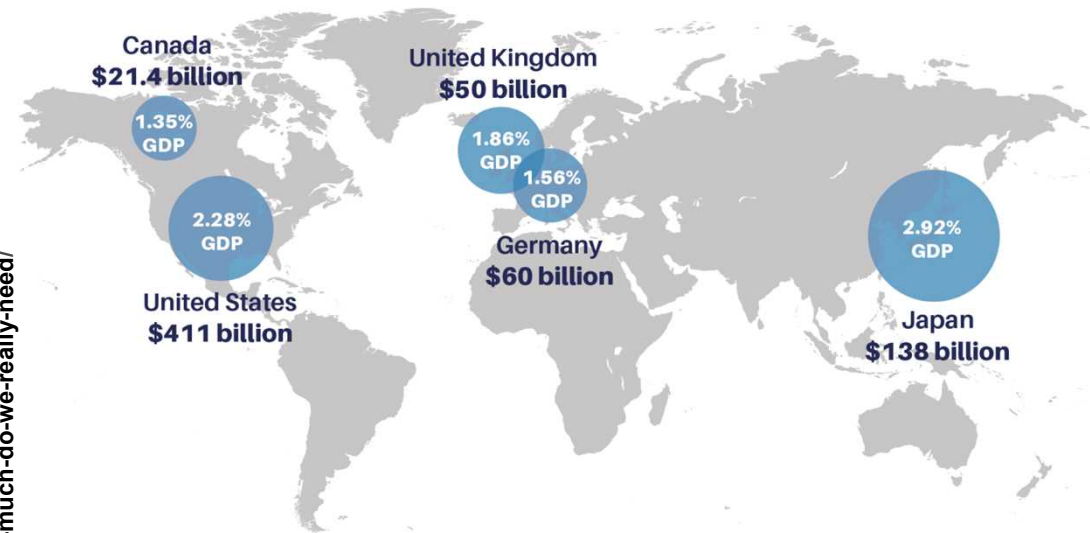
Project Goals in 2040 (3):

Economic and social impact of sleep debt

Japan loses ~15 trillion yen annually due to insufficient sleep (worst in developed countries per GDP)



<https://www.weforum.org/agenda/2019/04/which-countries-get-the-most-sleep-and-how-much-do-we-really-need/>



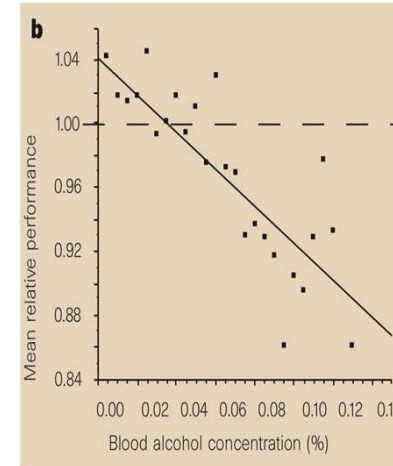
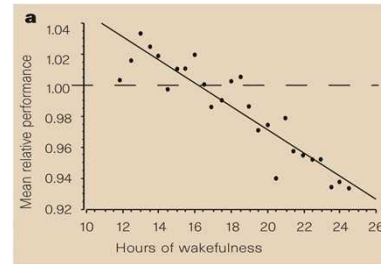
Hafner *et al.* (2016) "Why Sleep Matters – The Economic Costs of Insufficient Sleep: A Cross-Country Comparative Analysis"

Data from RAND Europe survey

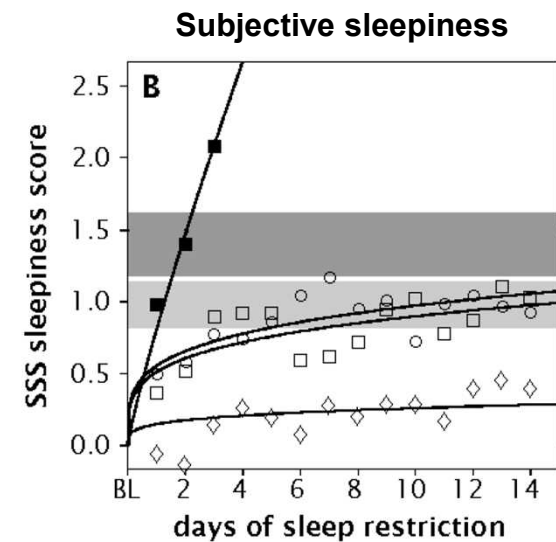
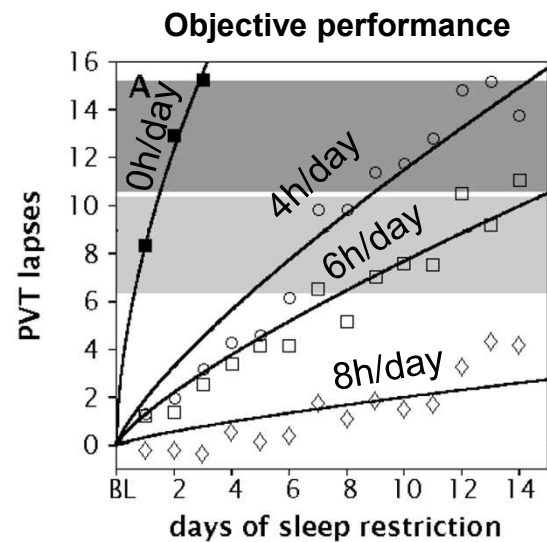


Project Goals in 2040 (4):

Effects of insufficient sleep on performance



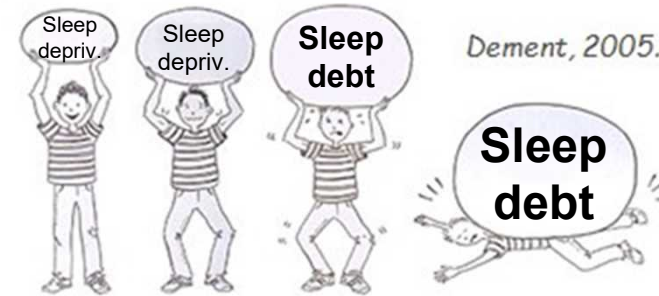
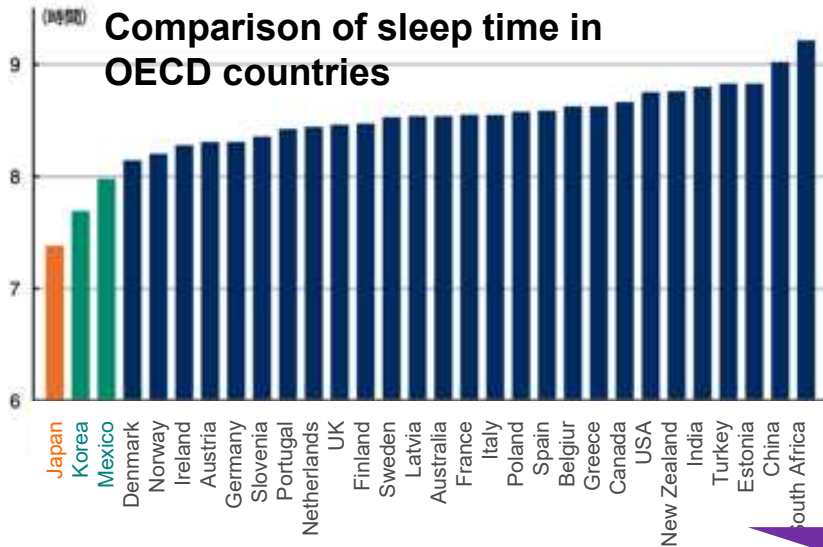
Dawson, D. & Reid, K. *Nature* 388:235 (1997)



Van Dongen, Dinges, et al. *Sleep* 26:117-126 (2003)

Project Goals in 2040 (5):

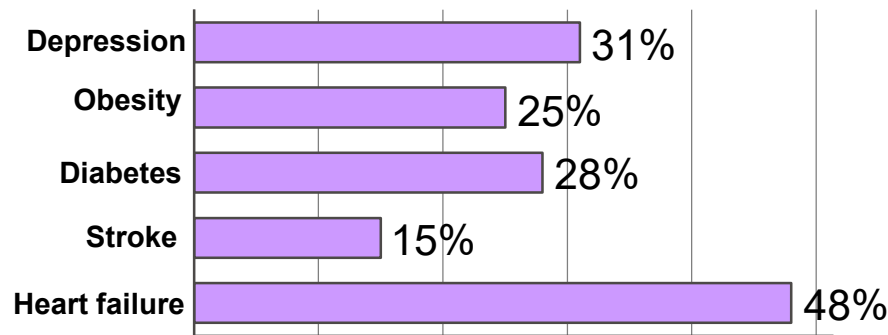
Sleep debt increases risk of diseases



Sleep Debt = Accumulated sleep deprivation

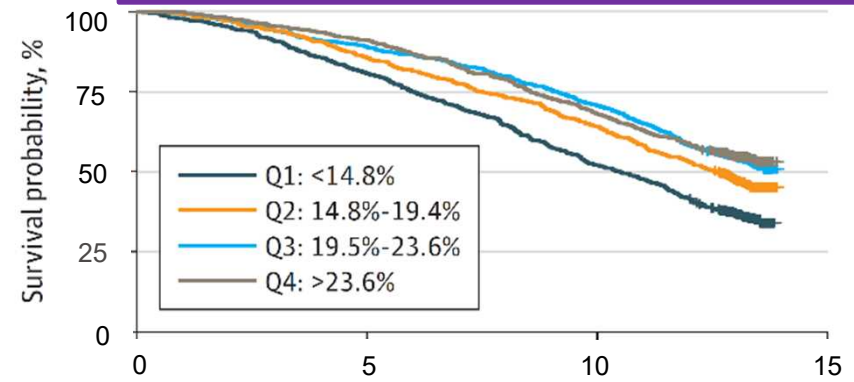
- Breakdown of CNS-immune system crosstalk
- Dysregulation of autonomous nervous system and endocrine system

Increase in diseases risks with daily sleep time < 7 h



Kecklund & Axelsson, 2016

Increase in mortality rate with reduced REM sleep



Follow-up time (y) Leavy et al., 2020

Project Goals in 2040 (6):

Possible application of artificial hibernation to emergency and critical care medicine



Active period



Ictidomys tridecemlineatus

400 Heart Rate <10
200 Respiration rate 1~5
37°C Body temperature 5°C

Hibernation period



O₂ consumption and energy metabolism **reduced to 13%**



Application of synthetic hibernation to humans



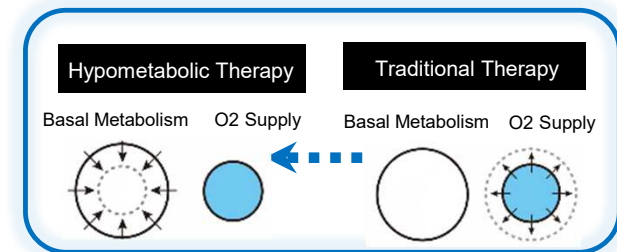
Reduced tissue oxygen consumption



Life-saving medical care for myocardial infarction / stroke / ischemia / traumatic shock / severe infectious diseases (COVID-19, etc.)



Suppression of inflammation, immune response, shock, tissue damage, and cell damage is expected



Project Goals in 2040 (7): Our MS project achieves...

R&D Goal 1

Technologies to
manipulate sleep need
set-point

R&D Goal 2

Technologies to prevent
diseases caused by
sleep debt

R&D Goal 3

Disease risk prediction and
prevention based on sleep

R&D Goal 4

Nationwide expansion of
sleep medicine network

R&D Goal 5

Synthetic hibernation
technology



Economic effect of
~10 trillion yen / year



Long and healthy lives freed up
from sleep problems



Reduce mortality and morbidity
in emergencies and disasters



Interplanetary flights and
exploitation into space

Five R&D goals to achieve Moonshot sub-objectives 1 and 2

Major goal of MS7 : Realization of sustainable care systems to overcome major diseases by 2040, for enjoying one's life with relief and release from health concerns until 100 years old

Sub-objective 1: Realization of a society where everyone can prevent diseases spontaneously in daily life

Sub-objective 2: Realization of a medical network accessible for anyone from anywhere in the world

R&D Goal 1: Release from the strict needs of sleep time

R&D Goal 4: Make sleep healthcare networks accessible anytime and anywhere even under disasters

R&D Goal 2: Prevention of the disease onset/progression caused by sleep debt

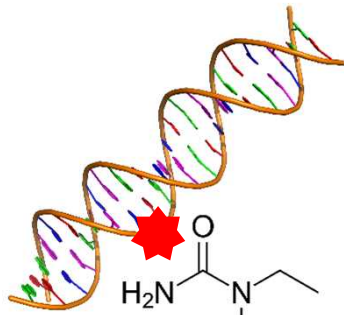
R&D Goal 5: Reduce mortality and sequelae drastically by synthetic hibernation

R&D Goal 3: Prediction of the disease onset/progression caused by sleep debt



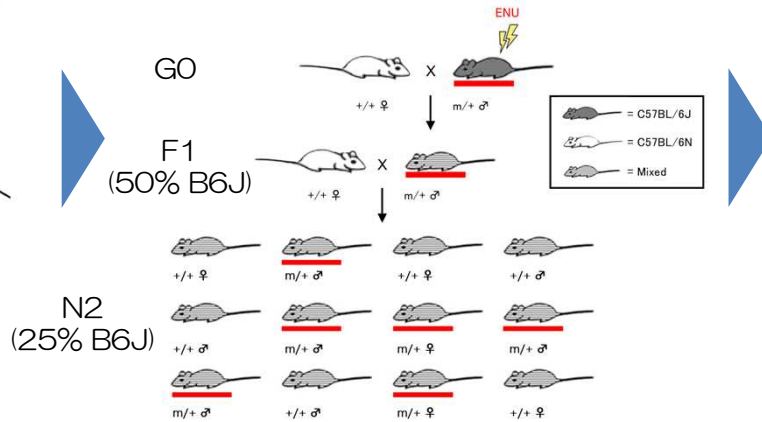
Research breakthroughs from IIS (1) :

Discovery of genes regulating sleep : *Sleepy (SIK3)* and *Dreamless (NALCN)*



Random Mutagenesis with ENU

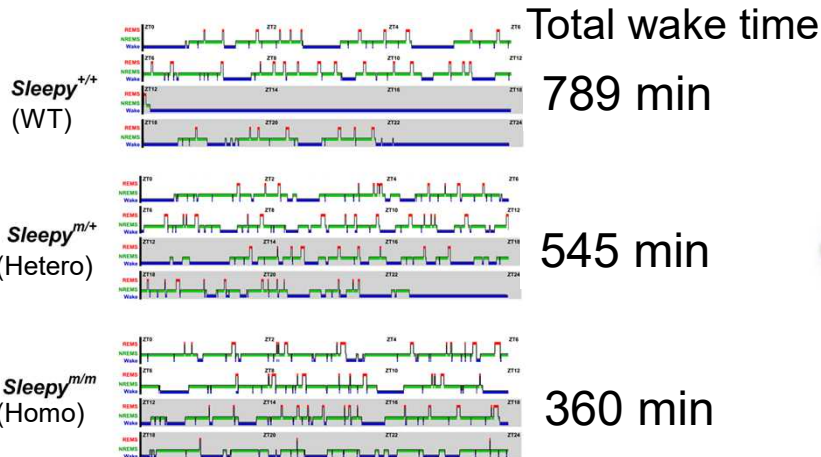
Mapping of mutant genes



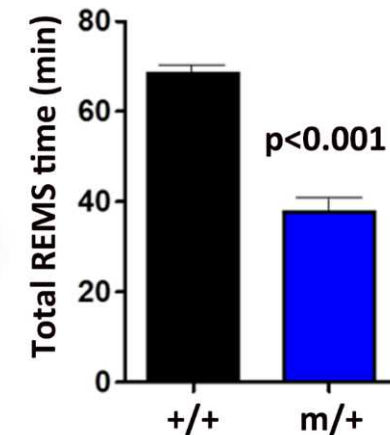
Screening of sleep phenotype > 8,000 mice



Sleepy Mutant mouse



Dreamless Mutant mouse

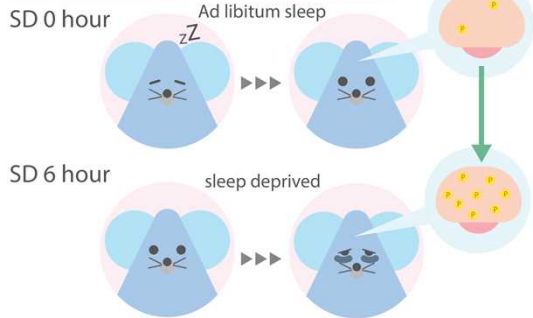


Funato et al., *Nature* 2016

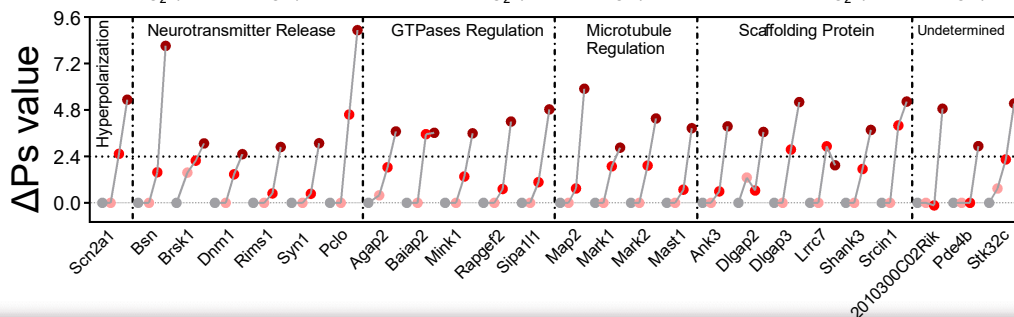
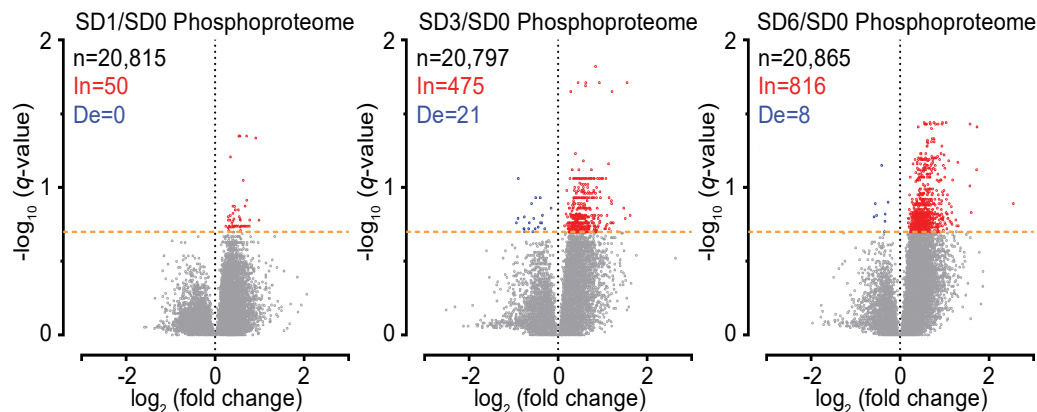
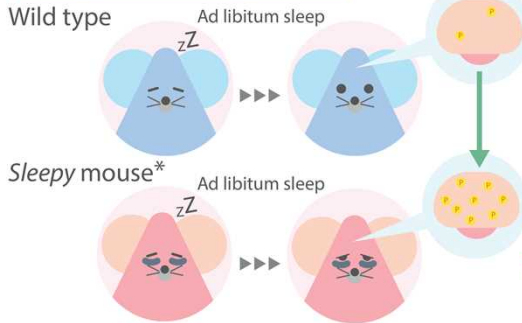
Research breakthroughs from IIS (2) :

SNIPPS: Molecular substrates of sleep need

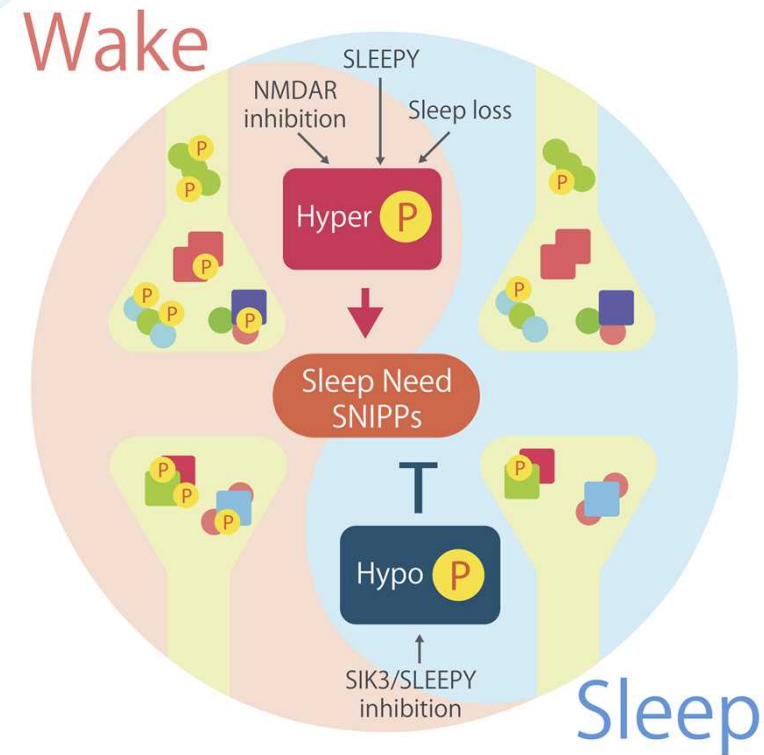
Slept versus Sleep-deprived mouse



Wild type versus Sleepy mouse



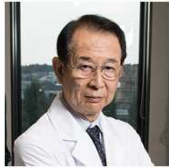
Molecular signatures of synaptic homeostasis and sleep/wake homeostasis



Wang et al., Nature 2018

Research Breakthroughs from IIS (3) :

Mechanistic therapy of narcolepsy with orexin agonists



HTS for OX₂R agonists and optimization of selected hits

Identification of OX₂R as drug target for narcolepsy treatment

Discovery of orexin and study of orexin KO mouse phenotype



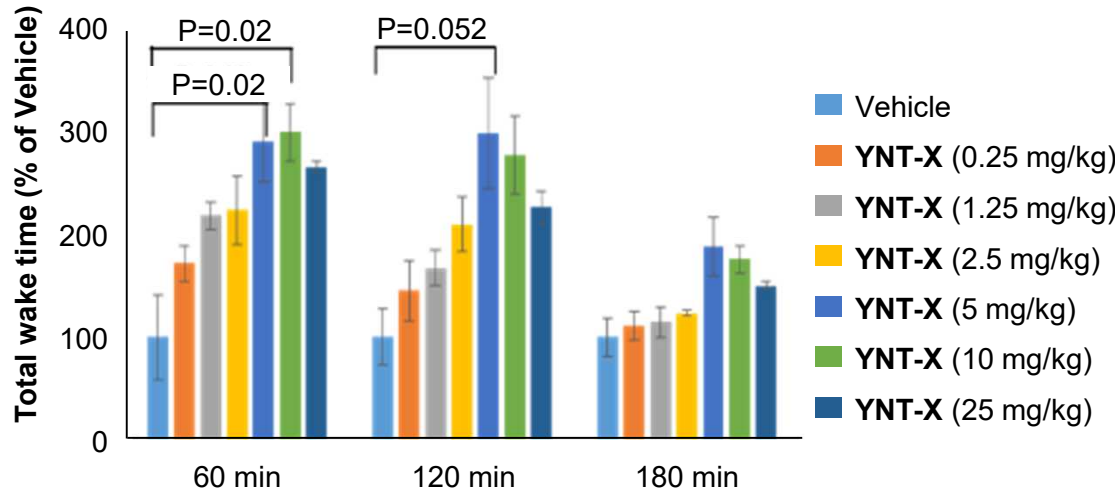
Identification of the first lead compound of OX₂R agonist (YNT-185)

Pharmacological assays and evaluation of physicochemical properties including PK

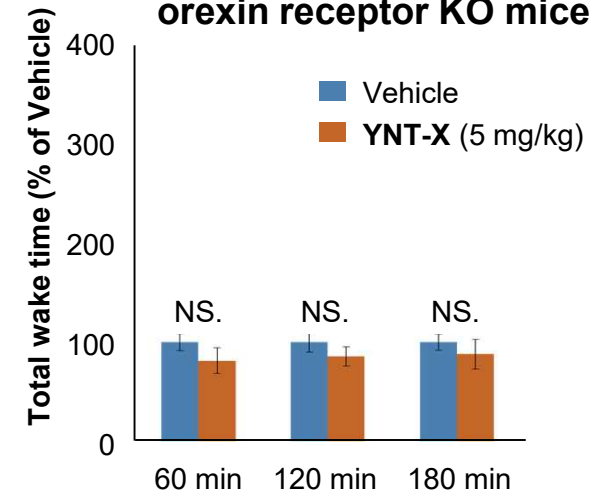
Further optimization of the lead structure

Identification of a development candidate (YNT-X)

PO arousal promoting effect in wild-type mice

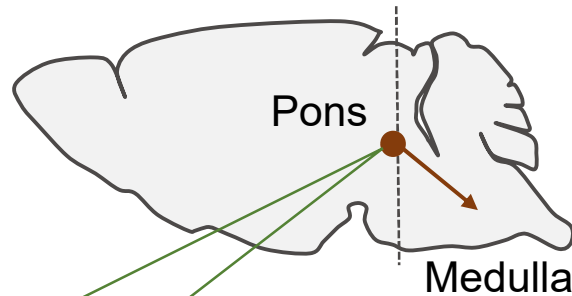


No arousal effect in orexin receptor KO mice

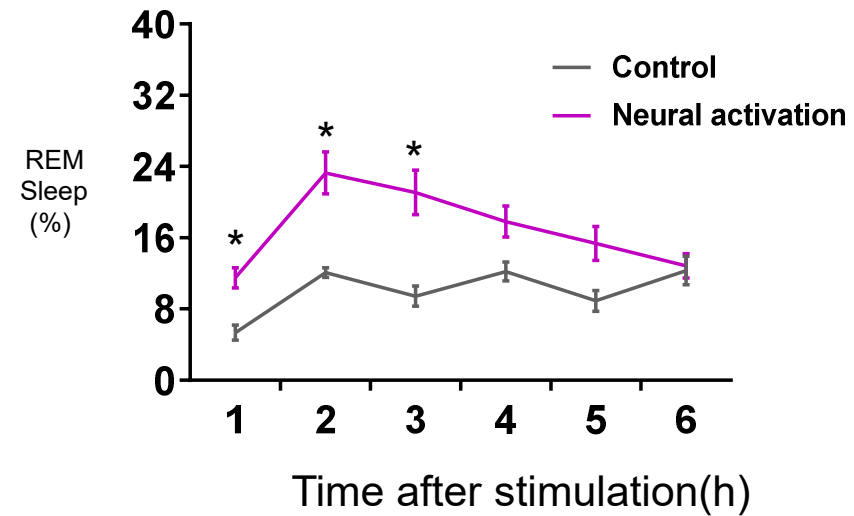
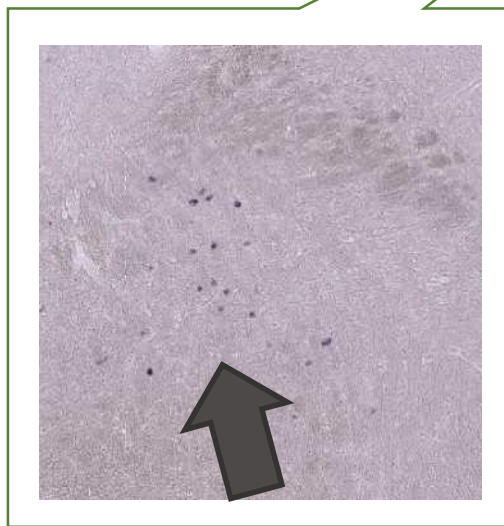


Nagahara et al., *J Med Chem* 2015; Irukayama-Tomobe et al., *PNAS* 2017; Unpublished

Identification of neural circuits regulating REM sleep



A subset of neurons in the pons that projects to the medulla induces REM sleep

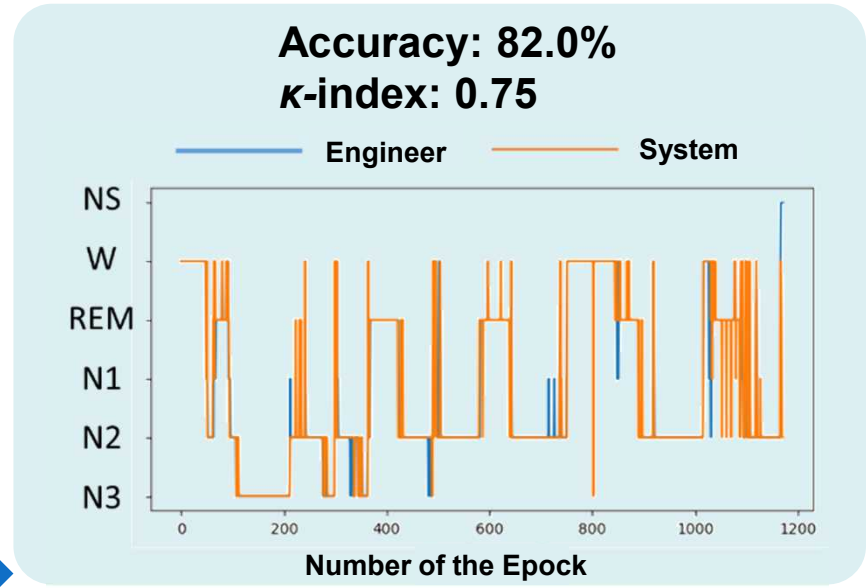
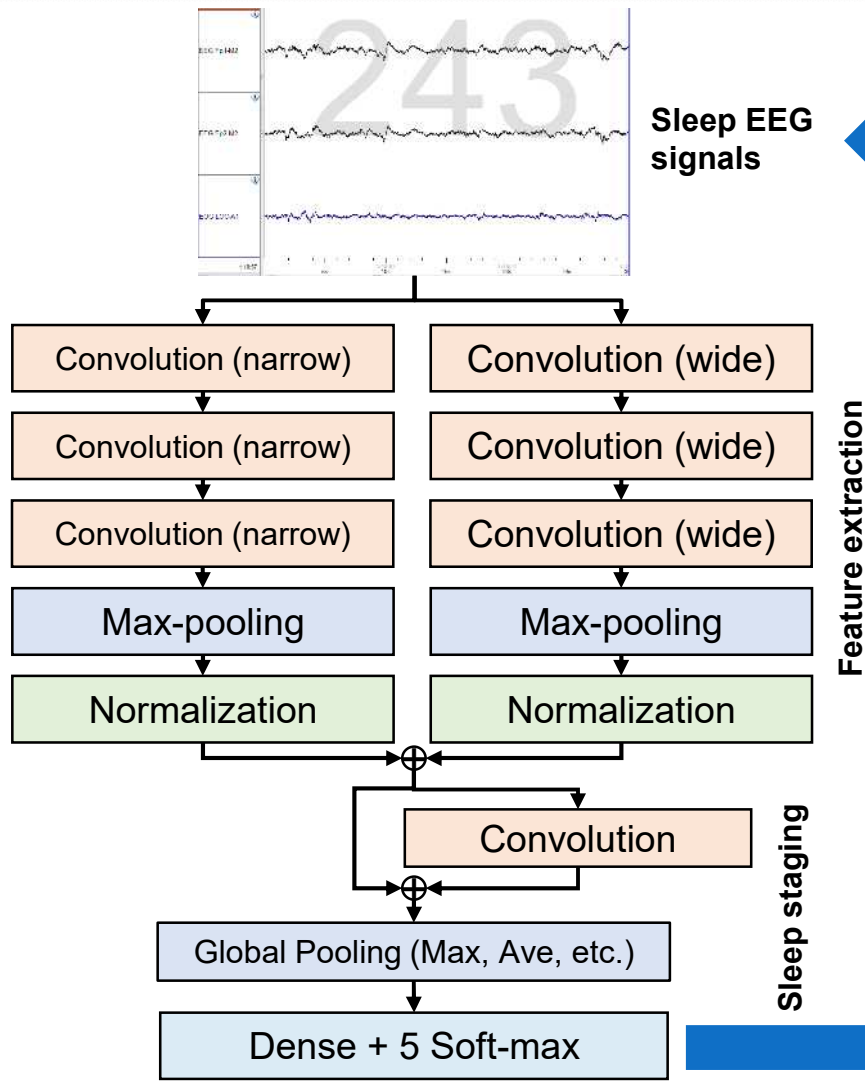


These neurons are very sparse and small in number, thus remained unknown for a long time. However, we finally succeed in identifying these REM sleep-specific neurons.

Artificial activation of these neurons strongly increases REM sleep!

Hayashi et al., *Science* 2015; Unpublished

Research Breakthroughs from IIS (5) : Development of in-home sleep EEG device and automatic sleep staging in cloud AI

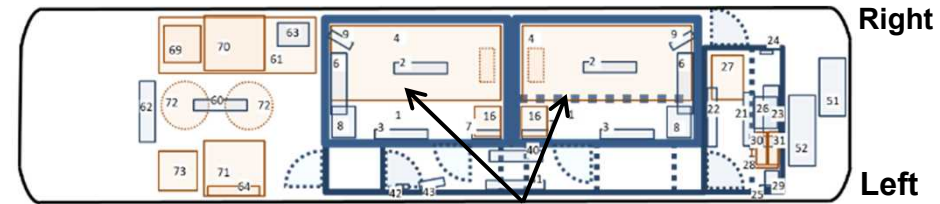


Yamabe et al., *Sci Rep* 2019

Research Breakthroughs from IIS (6) : Mobile sleep lab based on a fuel cell bus

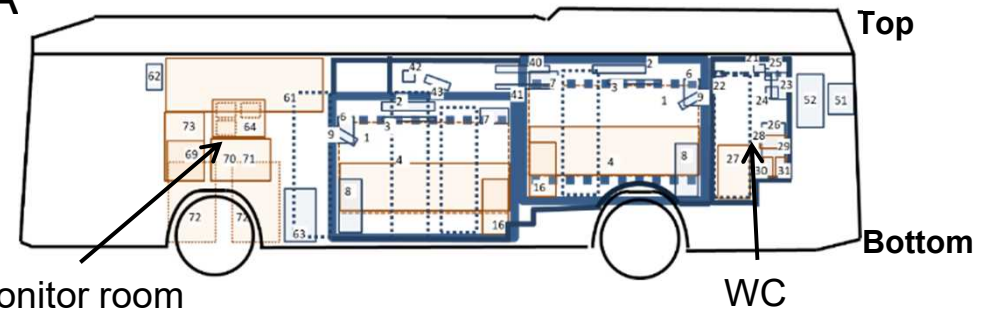


Converted fuel cell bus into a mobile sleep lab



Soundproof sleep measurement compartment (2 rooms)

Fuel cell bus in collaboration with TOYOTA



- Efficient power supply is possible for sleep recording (PSG test) without noise and vibration during parking.
- Monitor sleep in subjects/patients who live in various places all over Japan.



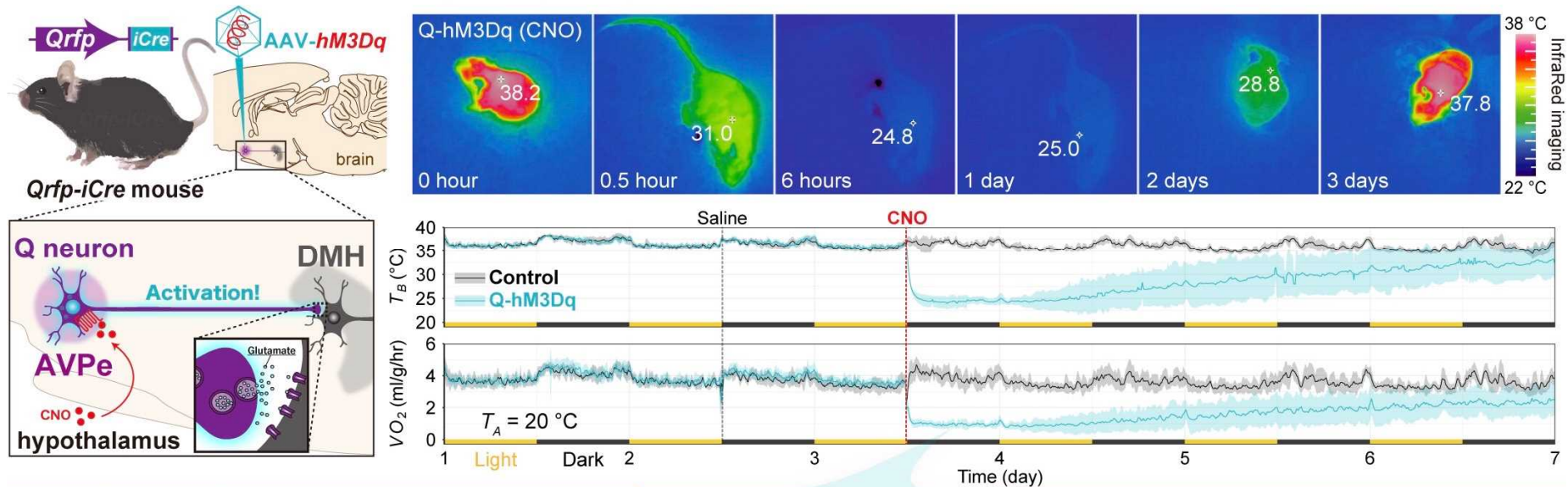
Standard method of human sleep recording: PSG test

"Toward the realization of Society 5.0 with the Tsukuba model"
Nature Digest, April 2020.

Research Breakthroughs from IIS (7) :

Discovery of a novel group of neurons that induces hibernation-like states in rodents

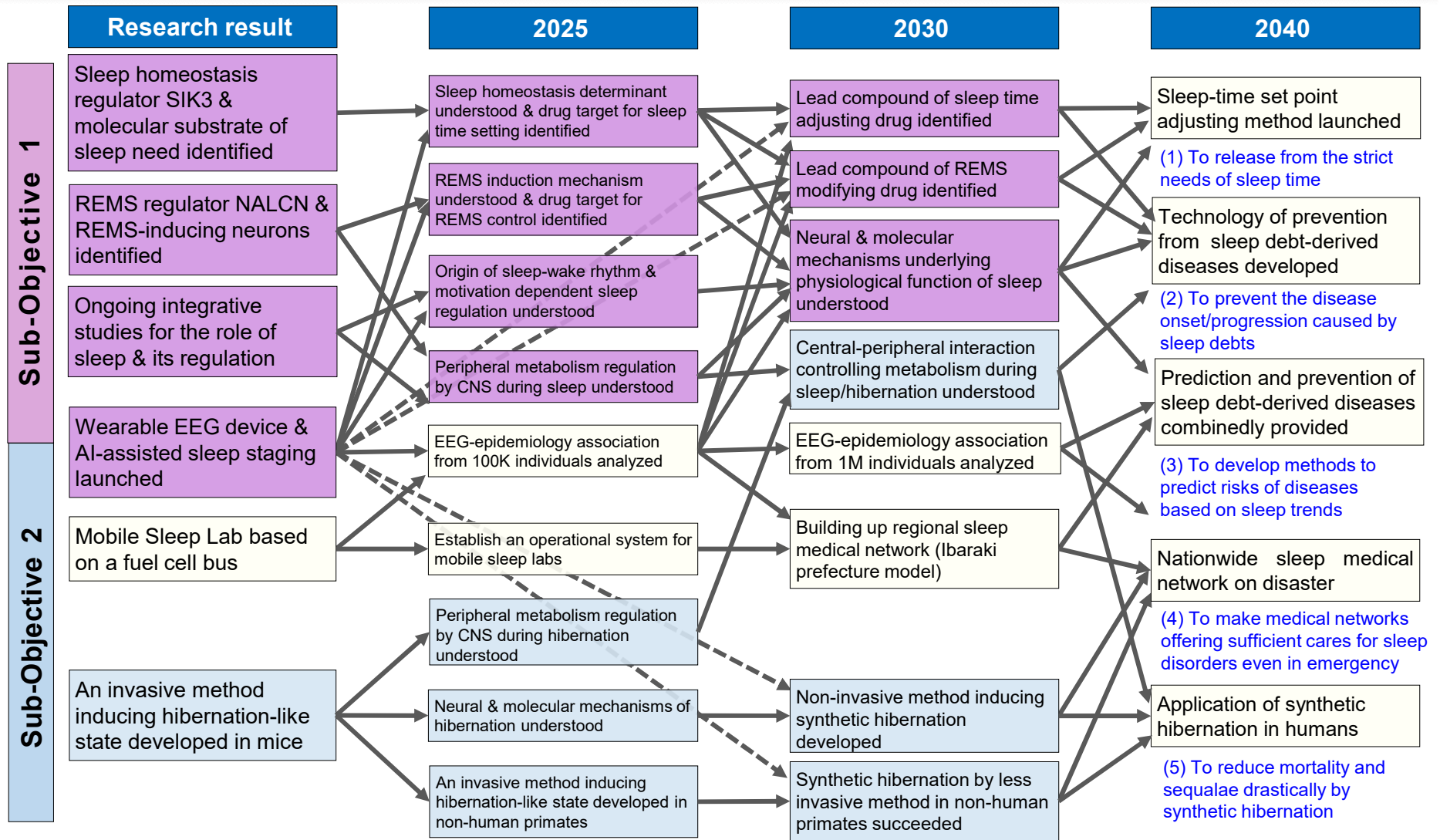
Takahashi et al., *Nature*, 2020



QH : Hibernation-like hypometabolic state



Milestones and R&D goals



R&D Goal 1 : Release from the strict need of sleep time

Practical use of sleep-time set point adjustment technology*



Discovery of sleep regulatory genes by large-scale human genetics research†



Gui de Chauliac Hospital



Sleep monitoring with the wearable device in home

Identify families with extreme sleep phenotypes†



University of Tsukuba

\$1,000-genome-analysis



Precision Medicine Development Center

Mouse reverse genetics for validation

Big data analysis



Laboratory Animal Resources Center



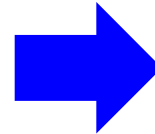
Center for Computational Science

*Breakthrough, †Milestone

R&D Goal 1 : Release from the need of sleep

Technology to manipulate sleep-time set point*

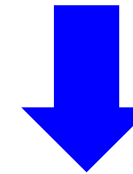
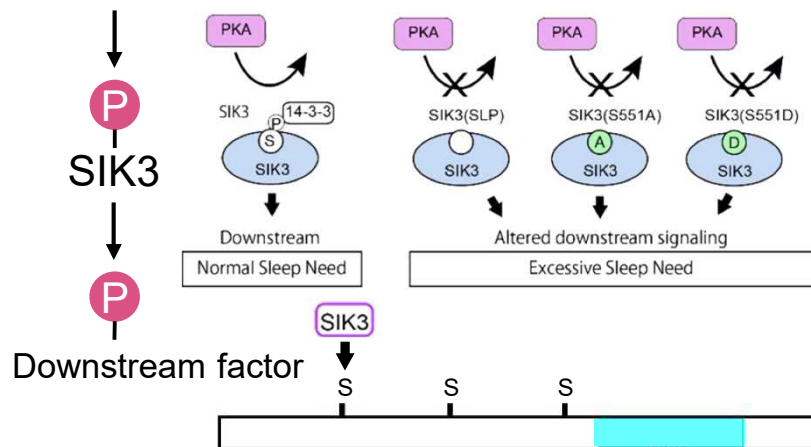
Elucidation of the molecular mechanism of sleep homeostasis†



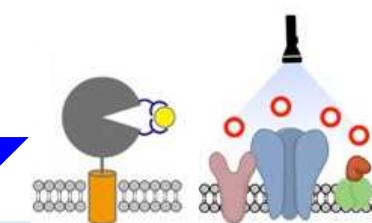
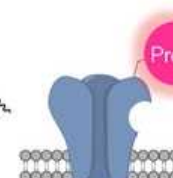
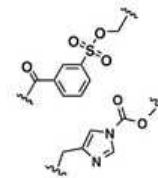
Discover suitable target molecules (GPCRs, enzymes, nuclear receptors, etc.) and markers for intervention†

Clarification of SIK3 signaling pathway

Upstream factor



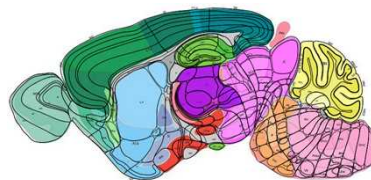
Development of lead compounds, antibody, virus vector



Conducted non-clinical development and clinical trials of sleep-time set point adjustment technology†

Identification of the neuronal groups and networks responsible for sleep homeostasis

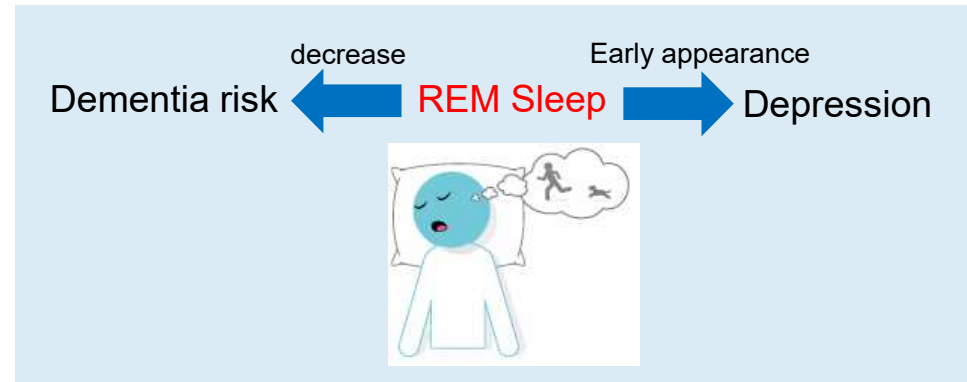
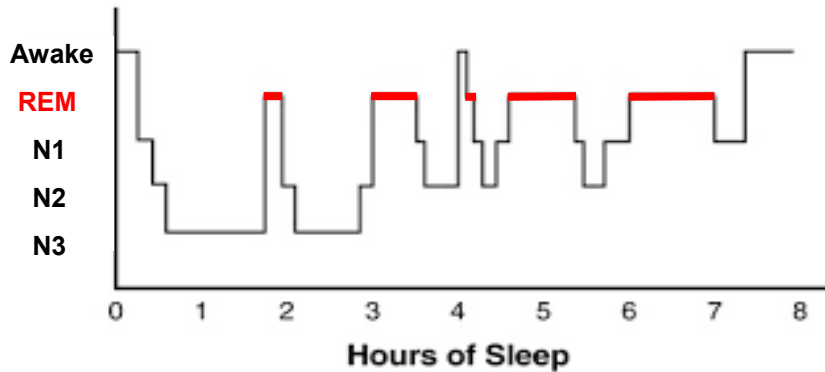
- Cell type specific Cre
- Virus Vector Cre



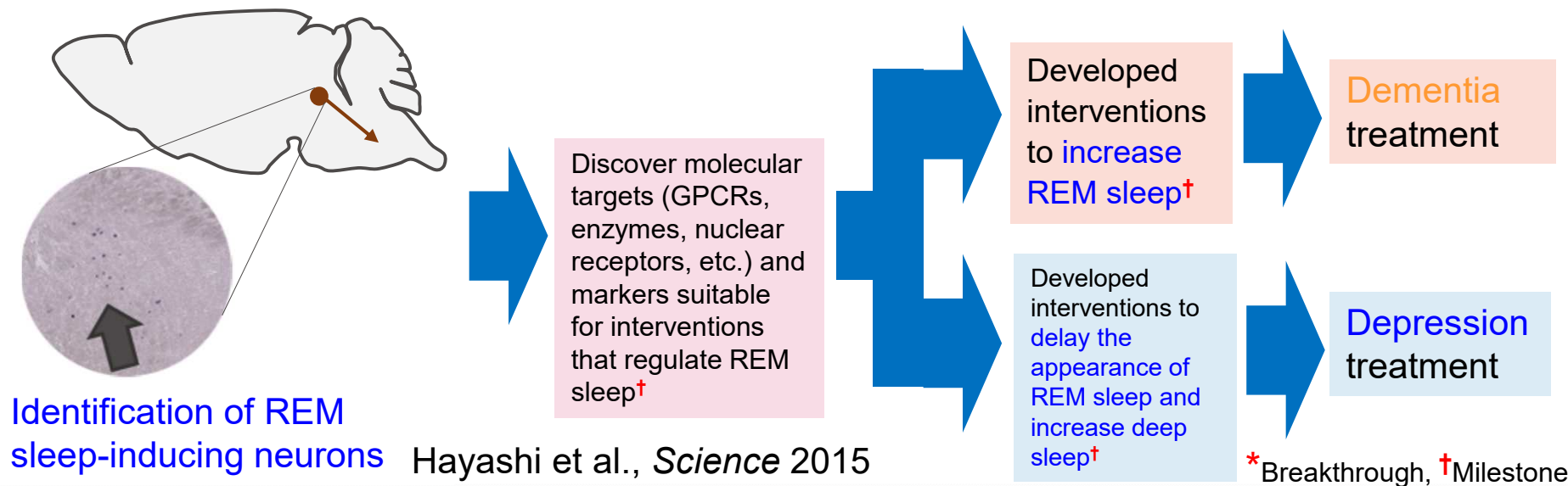
*Breakthrough, †Milestone

R&D Goal 2 : Realizing a society free from sickness due to sleep debt

Preventive technology for the disease onset/progression caused by sleep debt*



REM sleep, which tends to decrease with age, can be at risk for dementia if it decreases excessively, while patients with depression have its shorter latency.



R&D Goal 3 : Sleep trend-driven tailor-made preventive care

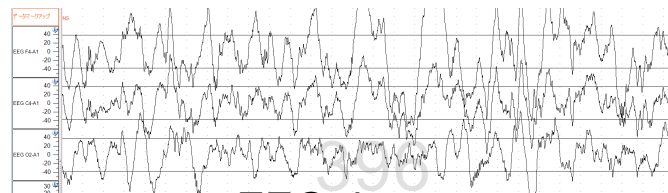
Disease risk prediction and preventive technologies*



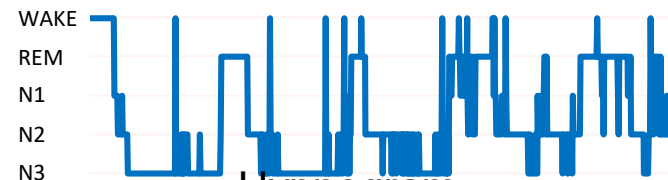
Medical checkup



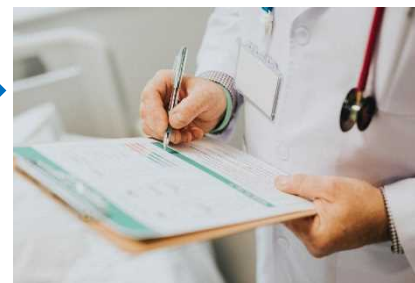
Sleep test at home (optional test)



EEG data



Hypnogram

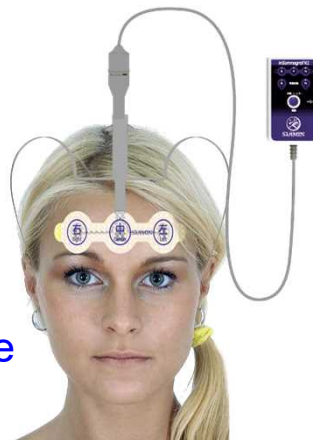


Medical records

Big data construction†
(100,000 – 1,000,000) of sleep and epidemiology



In-home sleep measurement system (wearable EEG device / EEG analysis by AI) developed by a venture company of IIS



Development of a risk prediction algorithm for diseases caused by sleep disorders†

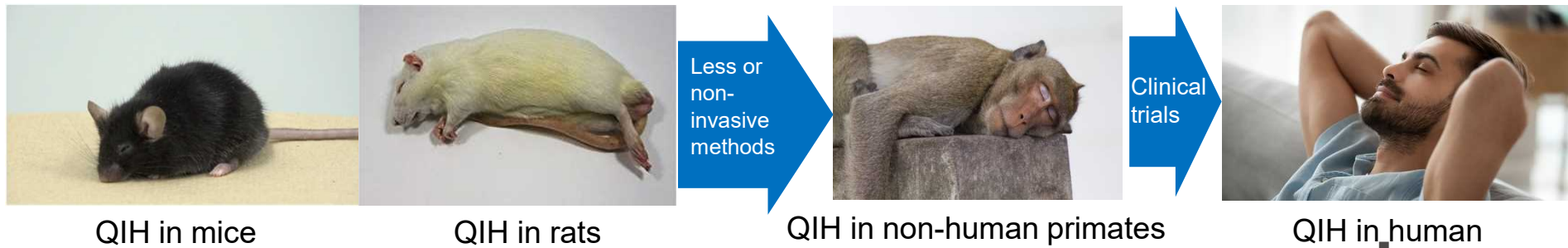
*Breakthrough, †Milestone

R&D Goal 5 : Reduction of mortality & morbidity in emergency and critical care through synthetic hibernation



Application of synthetic hibernation technology* (1)

Applying Q-neuron-induced hypothermia / hypometabolism (QIH) to primates† and even to humans†



Clinical application of short-term QIH beneficial for critical care†



Enables manned planetary exploration by long-term QIH (synthetic hibernation)

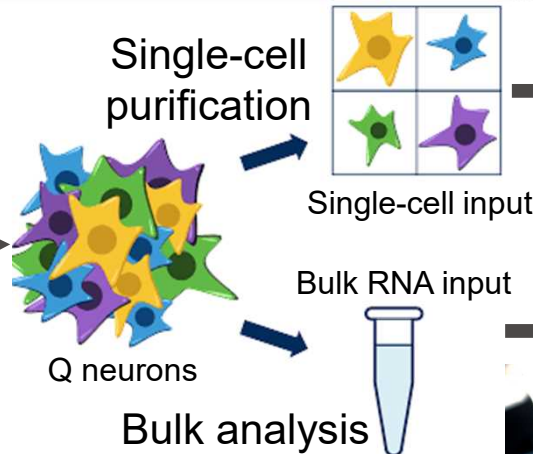
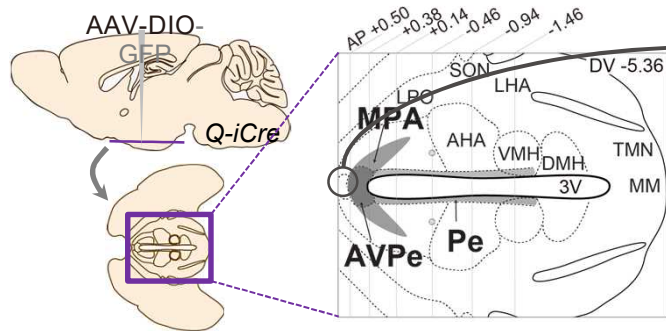


*Breakthrough, †Milestone

R&D Goal 5 : Realizing a society where mortality & sequelae can be dramatically reduced by synthetic hibernation

Application of synthetic hibernation technology* (2)

Identification of novel hypothalamic neurons (Q neurons) inducing hibernation



vs
 Identification of signal molecules, receptors (GPCRs, enzymes, nuclear receptors, etc.) and markers for intervention†



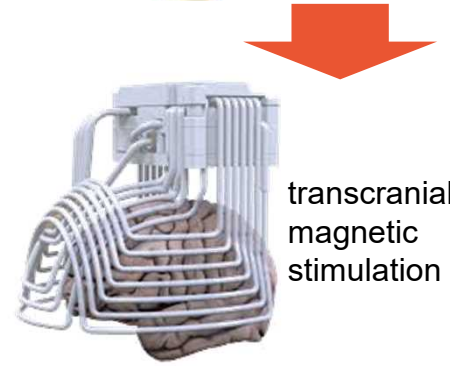
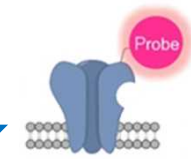
High throughput screening

Lead compounds, antibodies, viral vectors etc. acting on target†

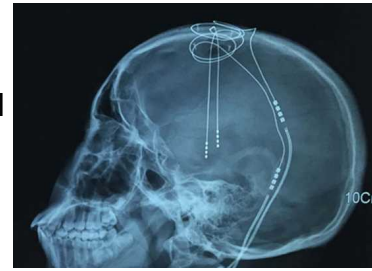


Medicinal chemistry

Applying non-invasive methods inducing synthetic hibernation for clinical trials†



transcranial magnetic stimulation



Deep brain stimulation

Minimally invasive intervention† to induce hibernation (e.g., TMS, tDCS, DBS etc.) and conduct clinical trials†



*Breakthrough, †Milestone

Main site for MS project: WPI-IIS, Tsukuba

Yanagisawa/Funato Lab
Molecular Genetics of Sleep Regulation

Toda Lab

Sakaguchi Lab
Sleep & Brain Plasticity



Molecular Genetics & Neuroscience

Sakurai/Hirano Lab

Lazarus/Oishi Lab
Motivation & Sleep

Hibernation, Circadian Rhythms
Emotional Memory & Sleep

Kitagawa Lab

Data science of sleep

Liu/Sakurai Lab

Fear, Sex & Sleep



Greene/Vogt Lab

Neuronal Circuitry of Sleep

Honjoh Lab

Sleep/Wake Homeostasis

Hayashi Lab

REM Sleep, Evolutions of Sleep

Kanbayashi Lab

Clinical Sleep Research



Human Physiology



Medicinal Chemistry



Tokuyama Lab

Sleep & Metabolism

Abe Lab

Sleep Physiology

Nagase/Kutsumura Lab

Drug Design

Collaborators in Japan and around the world

Hibernation



Masayuki Matsumoto
Professor,
Laboratory of Cognitive
and Behavioral
Neuroscience,
Faculty of Medicine,
University of Tsukuba



Genshiro Sunagawa
Special Postdoctoral Researcher,
Laboratory for Retinal Regeneration,
RIKEN



Clifford B. Saper
Professor,
Beth Israel Deaconess Medical Center
Harvard University



Vladyslav Vyazovskiy
Associate Professor,
Oxford University



Akihiro Yamanaka
Professor,
Nagoya University



Qinghua Liu
Investigator
National Institute of
Biological science Beijing

Sleep

Mathematics/AI



Morimitsu Kurino
Professor
Keio University



Haruka Ozaki
Associate Professor,
Faculty of Medicine,
University of Tsukuba



Toshiyuki Amagasa
Professor,
Center for Computational
Science, University of Tsukuba



Hiroyasu Ando
Associate Professor,
Faculty of Engineering,
Information and Systems,
University of Tsukuba

