

Moonshot 7 Symposium 2022



Sleep and Hibernation ~Deciphering the Mysteries~

Director of International Institute for Integrative Sleep Medicine
Program Manager / Professor

Masashi Yanagisawa

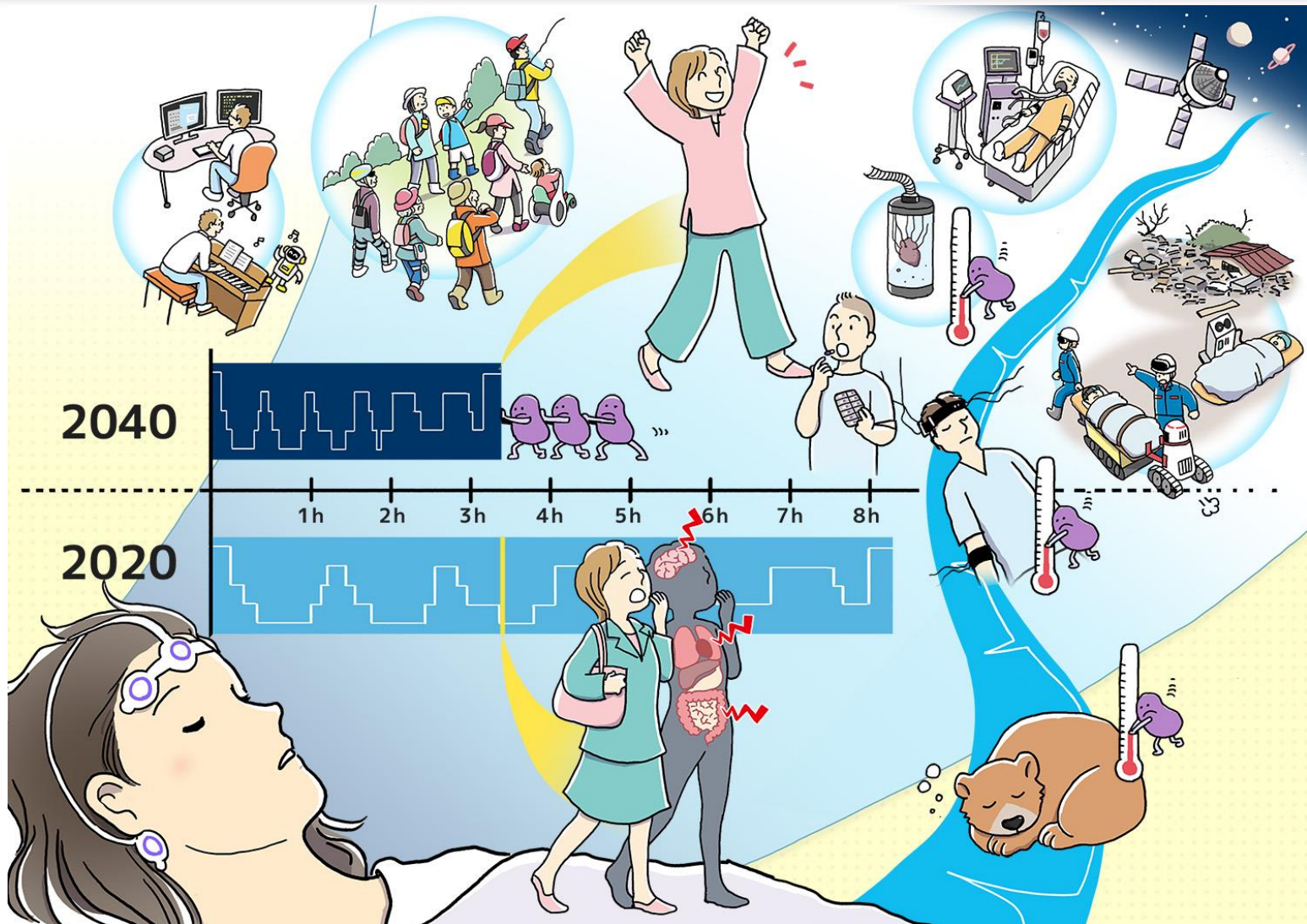
July 16, 2022

International Institute for Integrative Sleep Medicine

University of Tsukuba



Project's vision of society in 2040



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

Summary of project progress over the past year

R&D Goal 1

Freedom from sleep through healthy short sleep



Exploring intra-neuronal signaling pathways regulating non-REM and REM sleep

R&D Goal 2

A society that does not fall ill due to sleep debt



Clarification of REM sleep gating mechanism

R&D Goal 3

Tailor-made preventive medicine based on sleep trends



Development of EEG measurement device InSomnograf

R&D Goal 4

A society that provides access to sleep medicine anywhere, even in times of disaster



Mobile Sleep Lab: Development of a demonstration vehicle

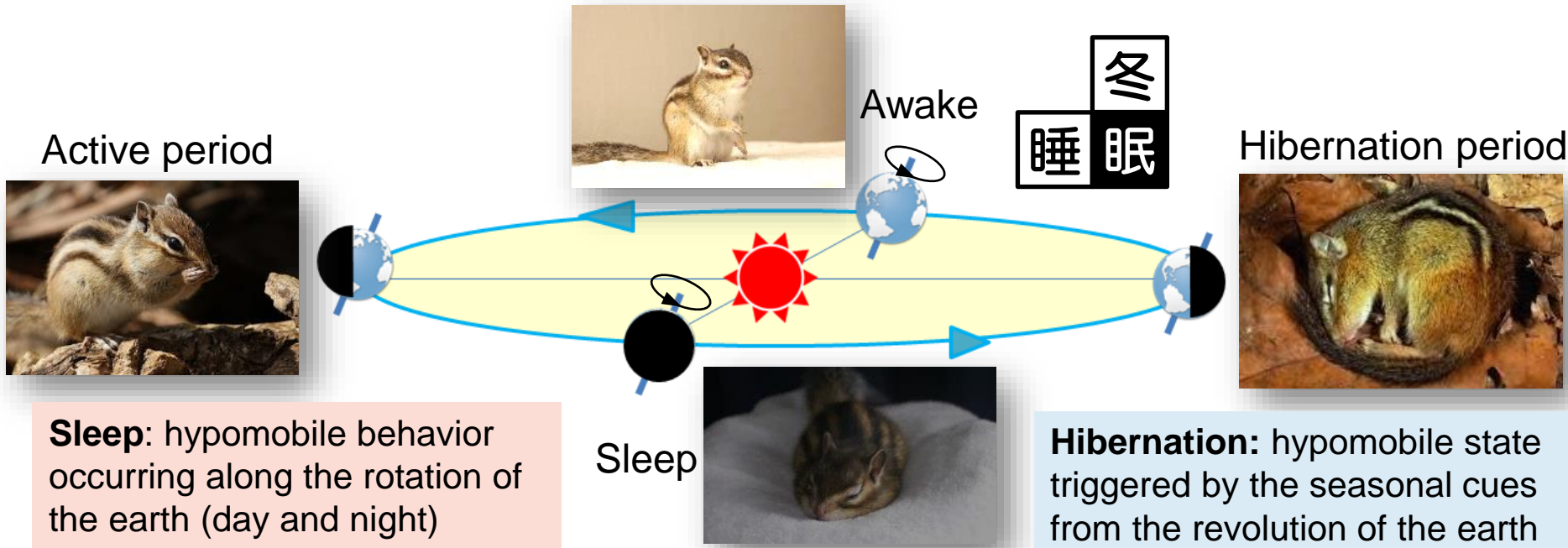
R&D Goal 5

Artificial hibernation technology can dramatically reduce mortality and aftereffects in emergencies and disasters



Development and Application of Induction of Hibernation-like Behavior Application

Sleep and Hibernation: Most challenging mysteries in neuroscience



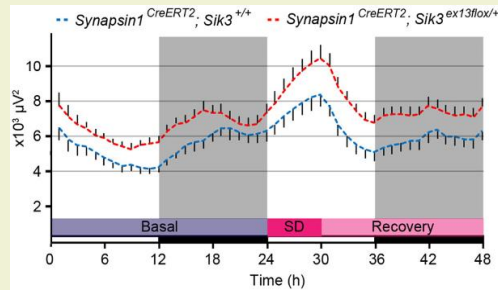
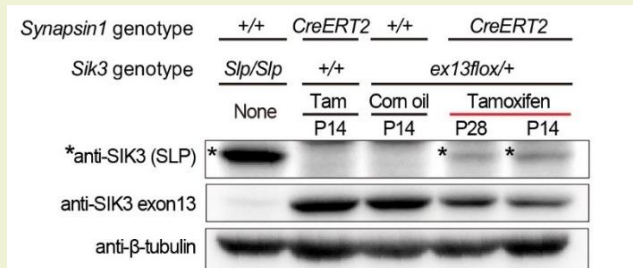
Sleep duration varies by species

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

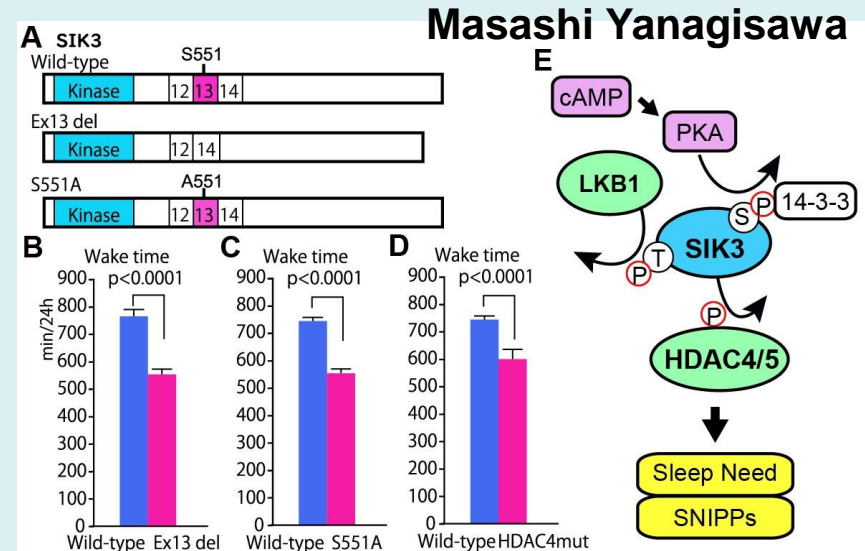
Order	Family	Number	Typical species
Primate	Cheirogaleidae	3	Fat-tailed dwarf
Carnivores	Bear family	4	Asiatic black bear, Polar bear (female only)
Rodents	Squirrel family	58	Thirteen-lined squirrel

Neural signal transduction regulating NREM and REM sleep



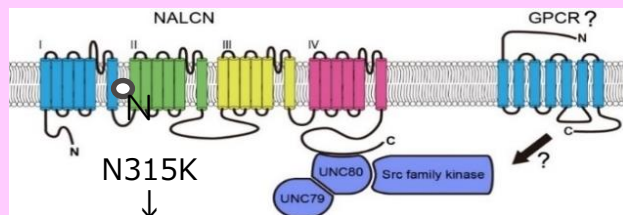
Mutant SIK3 in neurons after infancy increased sleep need (EEG delta power during NREM sleep)

Iwasaki et al. *J Neurosci* 2021



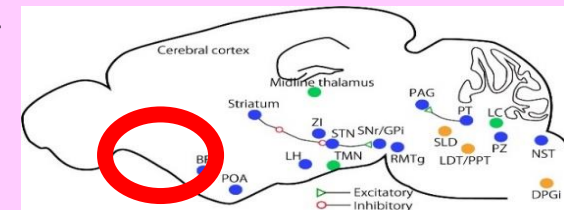
Progress has been made in elucidating the SIK3 pathway for NREM sleep regulation through gene-modified mice and viral vectors.

Honda et al. *PNAS* 2018, Wang et al. *Nature* 2018, Kim et al. *Nature*, in revision, Liu et al. *Nature*, in revision



Dreamless

Brain region-specific induction of gain- and loss-of-function of ion channel NALCN revealed the presence of REM sleep control sites (red circle) outside the brainstem

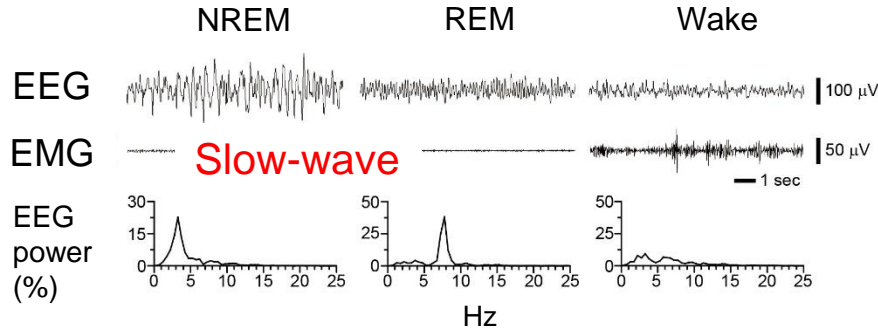
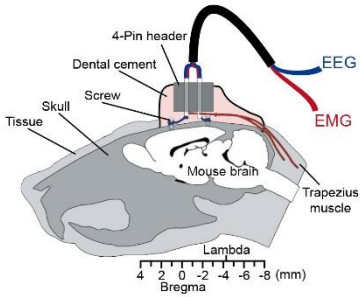


Funato et al. *Nature* 2016

Neural mechanisms for slow-wave generation

Sleep analysis in mice (EEG measurement)

Yo Oishi



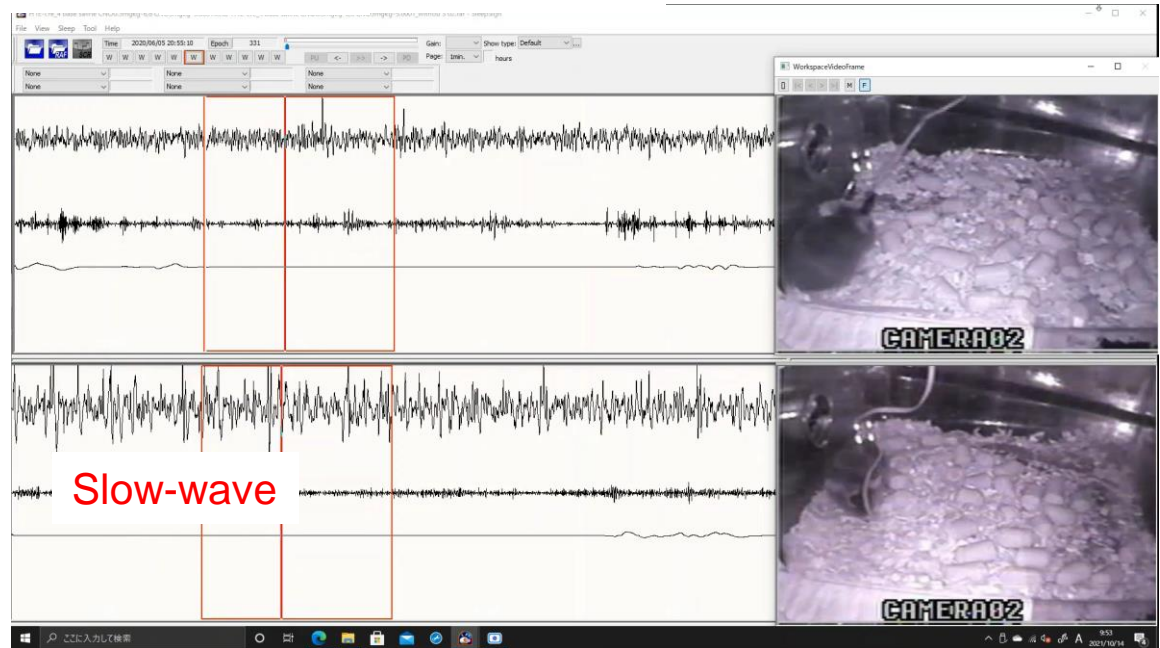
Mechanism of EEG shift to slow waves is unclear

Normal

H1 system-suppression

EEG
EMG
Locomotion

EEG
EMG
Locomotion



5 sec

REM sleep gating mechanism in mice

~Discovery of a new role for dopamine in amygdala~

Emi Hasegawa

Hasegawa, et al. *Science* 2022

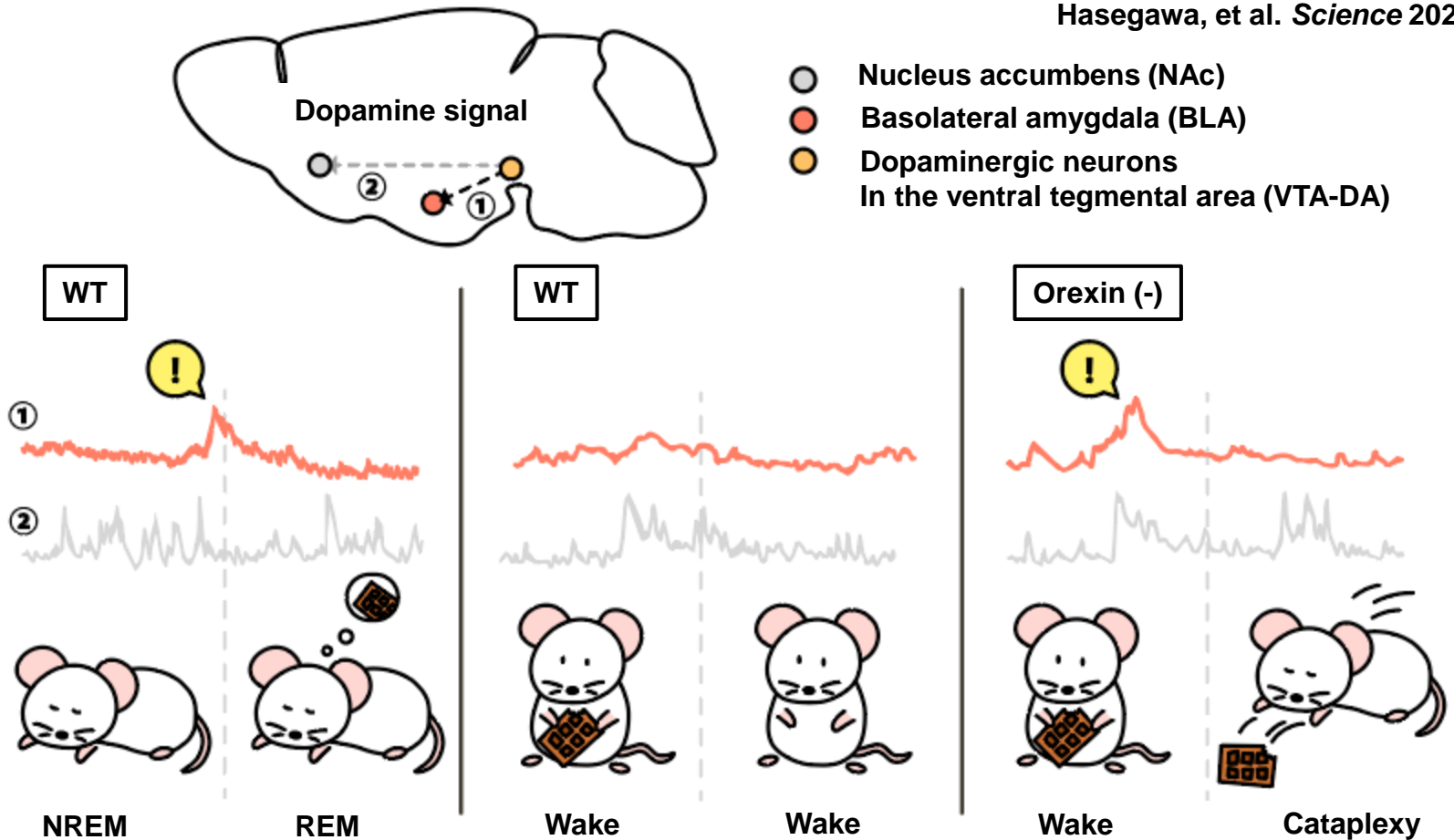
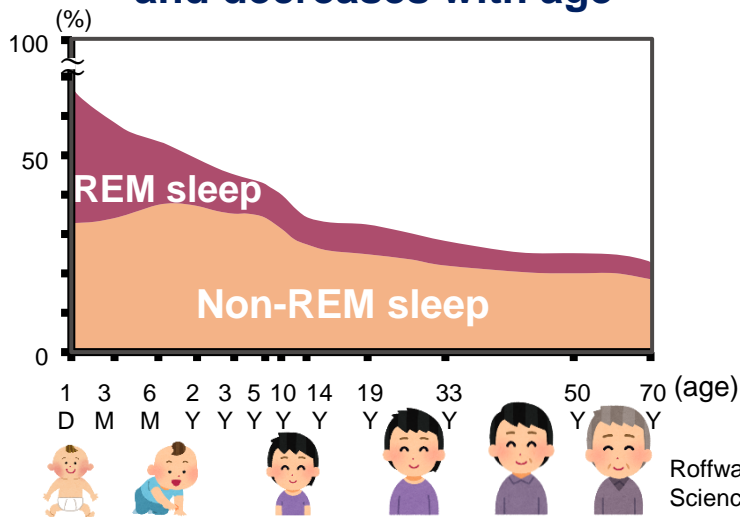


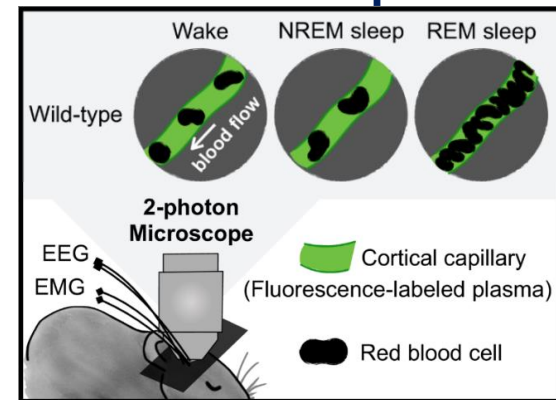
Illustration: Sara Kobayashi

Yu Hayashi^{1,2,3} (¹Univ. of Tokyo, ²WPI-IIIS, Univ. of Tsukuba, ³Kyoto Univ.)

REM sleep is abundant in neonates and decreases with age



Imaging blood flow in the brain during REM sleep



Upsurge of cortical capillary flow during REM sleep!

Tsai et al., Cell Reports, 2021

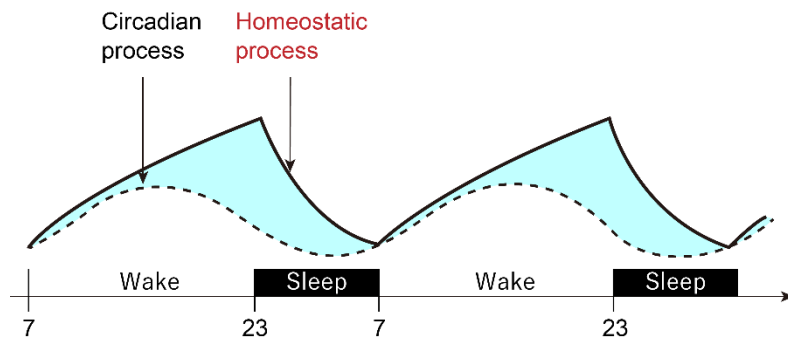
- ◆ REM sleep might be involved in maturation or aging
- ◆ Improving REM sleep might allow improving diseases

Discussion :

- REM sleep might be crucial for adequate material exchange in the enlarged mammalian cerebral cortex
- One reason people with less REM sleep are at higher risk for dementia might be reduced efficiency of substance exchange

Discovery of the neuron that measures wake duration and induces sleep

Sleepiness builds up during wake (homeostatic regulation)

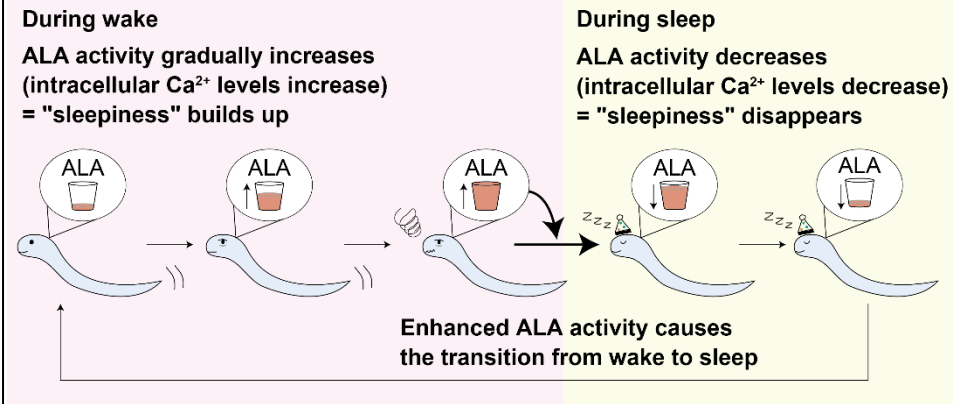


Modified from Daan et al., Am J Physiol., 1984

It is unclear where and how sleepiness accumulates

- ◆ Understanding the homeostatic regulation of sleep leads to developing treatments for sleep disorders

Search for neurons whose activity reflects duration of prior wake



ALA measures wake time and induces transition to sleep

Miyazaki et al., iScience, 2022

Discussion :

This ALA function requires a gene called *ceh-17*, which is conserved in mammals. The gene may be a clue to unraveling the mechanism of homeostatic control in mammals.

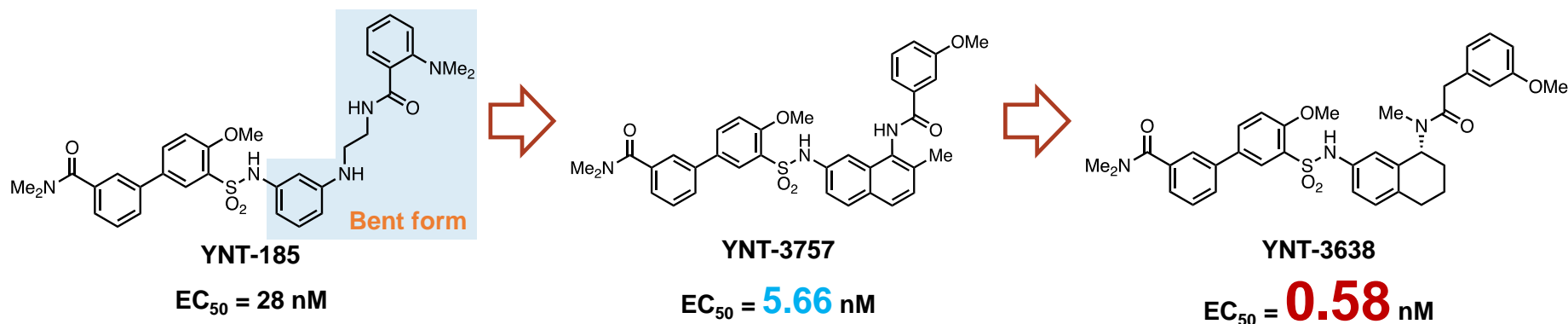
Development of Orexin Receptor Agonists

Narcolepsy

- Patients feel excessive daytime sleepiness (EDS), cataplexy, vivid dream-like images, hallucinations, as well as sleep paralysis.
- Because dysfunction of orexin/OX₂R system causes narcolepsy, OX₂R agonists have been expected to be a chemotherapeutic agent of narcolepsy.

【Purpose of this work】

Development of potent orexin receptor agonists
based on YNT-185 active conformation



Steric constrain of YNT-185's active conformation successfully enhanced
OX₂R agonist activity by **50**-fold compared to YNT-185.

Tsuyoshi Saito

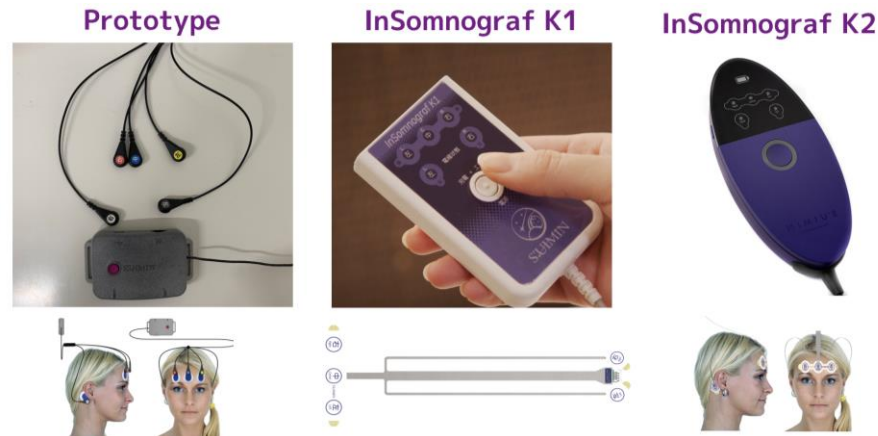


©National Geographic

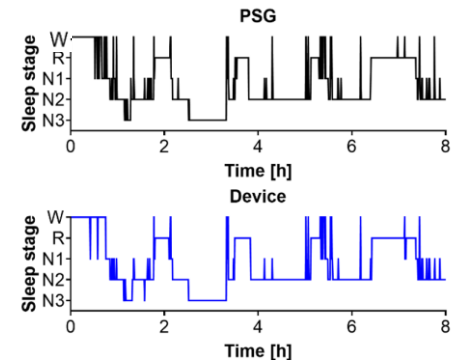
Development of EEG measurement device InSomnograf

Tetsuro Hiei

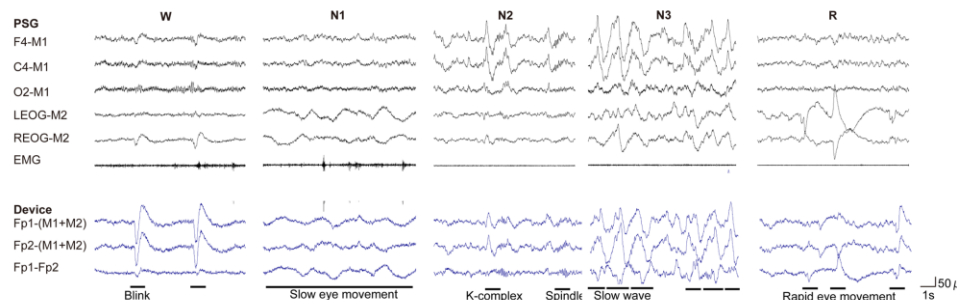
Achieved 86.9% agreement rate with PSG, a level comparable to existing medical device product



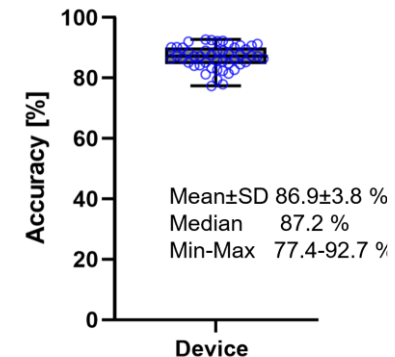
Hypnographic comparison



Raw EEG data



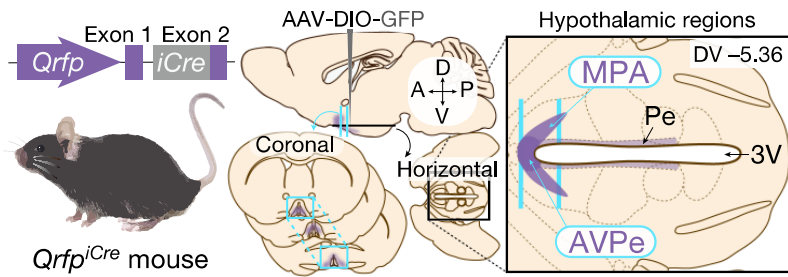
Match rate with PSG



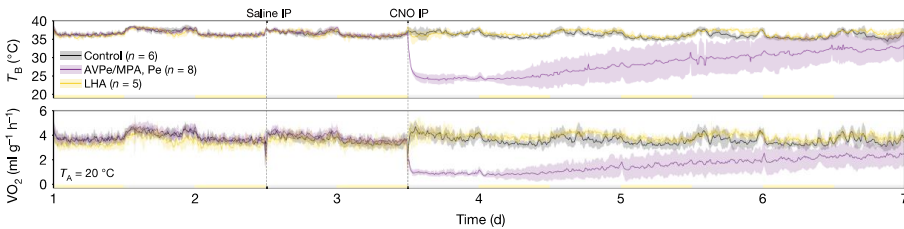
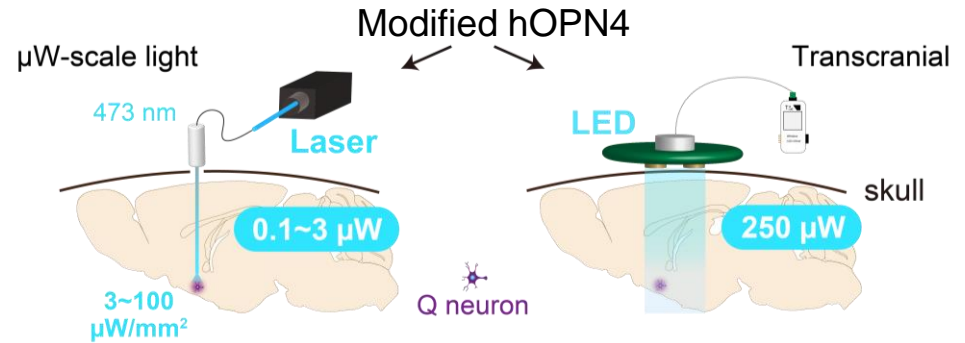
A new method to induce hibernation-like state (QIH) with high sensitivity and time resolution

Arisa Hirano

Conventional method to induce QIH



Control of QIH by novel optogenetic tool With high-sensitivity and high-time resolution

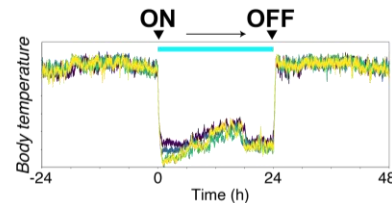


Mice take long time to recover from hypothermic state, which is distinct from natural hibernation

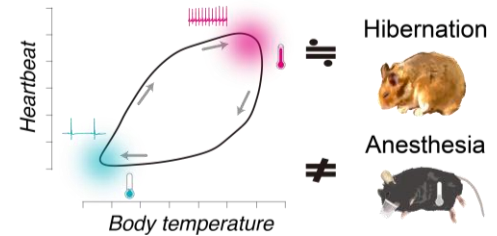
Takahashi, *et al.*, *Nature*, 2020.



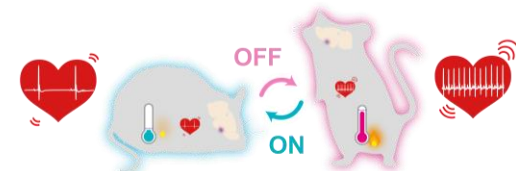
Sustainability for 24 hours



Similarity to Hibernation

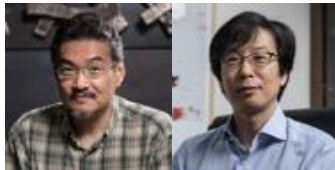


High Temporal Resolution



Takahashi, Hirano *et al.*, *in revision*.

Main crew still expands to accelerate world-class research

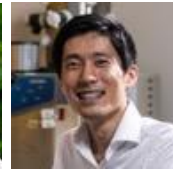


Yanagisawa/Funato Lab

Molecular Genetics of Sleep Regulation



Toda Lab



Sakaguchi Lab

Sleep & Brain Plasticity

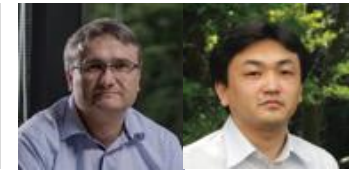


Molecular Genetics & Neuroscience



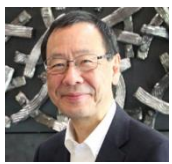
Sakurai/Hirano Lab

Hibernation, Circadian Rhythms
Emotional Memory & Sleep



Lazarus/Oishi Lab

Motivation & Sleep



Kitagawa Lab

Data science of sleep



Shi Lab



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/Okura Lab

Sports, Sleep & Metabolism



Abe Lab

Sleep Physiology



Kutsumura/Saito Lab

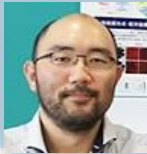
Drug Design

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



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



Vladyslav Vyazovskiy
Associate Professor,
Oxford University



Qinghua Liu
Investigator
National Institute of
Biological science Beijing

Sleep

Mathematics/AI



Morimitsu Kurino
Professor
Keio University



Toshiyuki Amagasa
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Center for Computational
Science, University of Tsukuba



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



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