Project Leader **Makoto Honda** Sleep Disorders Project

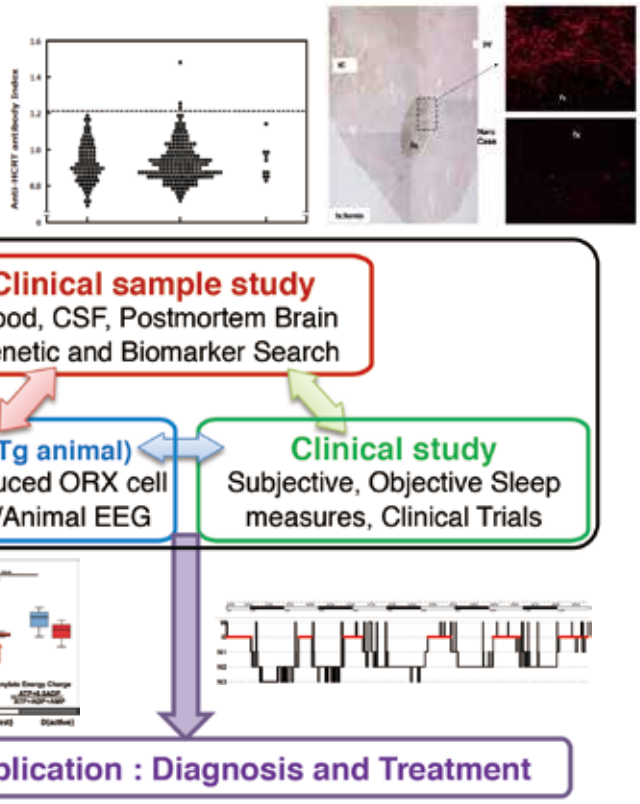
Narcolepsy and Hypersomnia:
Find the causes to develop better treatments

Narcolepsy is a sleep disorder with abnormal intrinsic sleep-wake regulation, resulting in unique symptoms including frequent lapses into sleep, nocturnal sleep instability and REM sleep related manifestations such as cataplexy (abrupt loss of muscle tone triggered by emotion), sleep paralysis and hypnagogic hallucination.
Narcolepsy is associated with a deficiency of wake-promoting orexin/hypocretin producing neurons localized in hypothalamus, and virtually all the patients carry *human leukocyte antigen (HLA)-DQB1*06:02.*

"We are trying to solve the mystery of narcolepsy: Listen to the patients, get the whole picture, and improve their lives"

Narcolepsy is associated with a variety of physical and psychiatric comorbid conditions. Since appropriate wakefulness is essential for higher brain functions, abnormal sleep-wake regulation can lead to various associated features. Despite the progress in sleep research fields, we currently have inadequate symptom-based-treatments for sleep disorders, including narcolepsy. We are trying to elucidate the pathophysiology of narcolepsy with multifaceted problems to improve the QOL of hypersomnia patients.

Research Strategy



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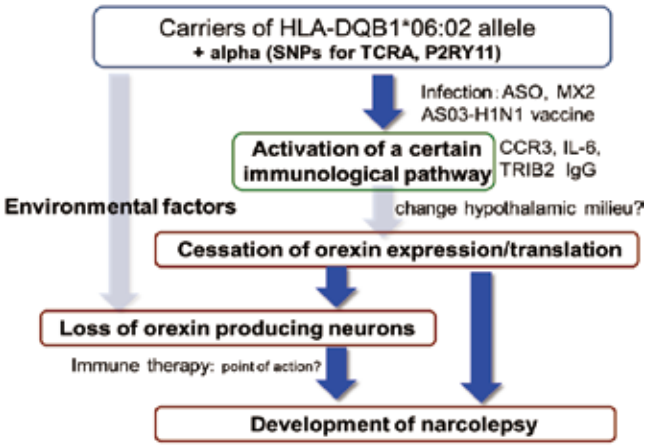
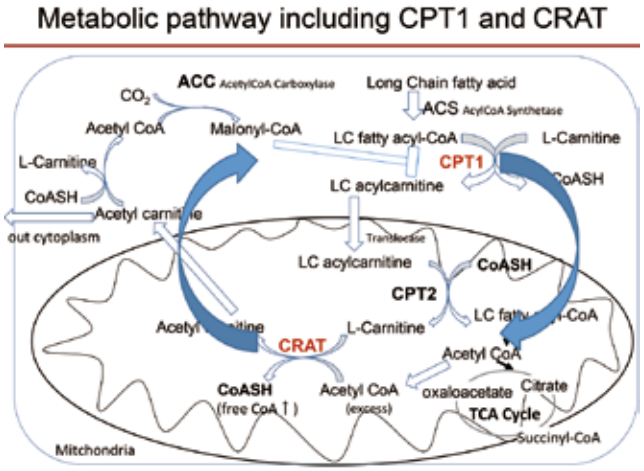
Research Interests

Hypothalamus works as a center for sleep-wake switch in coordination with the integrated information from the body. Among them, we have particular interests in immune and metabolic status, which can be the key to understand altered sleep-wake regulation in narcolepsy.

1. HLA association and immune abnormality

In addition to the tight association with HLA, narcolepsy is also associated with T cell receptor (TCR) alpha locus, indicating the HLA-TCR mediated immunological alterations. Both genetic and environmental factors are implicated in narcolepsy predisposition. We have reported the altered immune status in narcolepsy, but so far could not confirm the leading hypothesis that orexin neurons are destructed by direct autoimmune attacks. Immune mechanisms other than autoimmunity might lead to stop producing orexin neuropeptide.





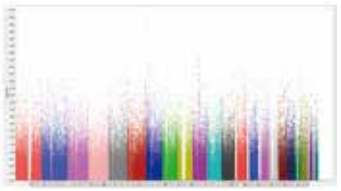
2. Metabolic aspect of narcolepsy and related hypersomnia

Through genome-wide association studies (GWAS), we have identified novel narcolepsy (and other hypersomnia) related genes. They are key enzymes located in the pathway of fatty acid metabolism. We confirmed their functional relevance, performed the clinical trials, and analyzing the potential efficacy of the novel therapy (promoting metabolism) in hypersomnia patients.

Members of Sleep Disorders Project (2017)

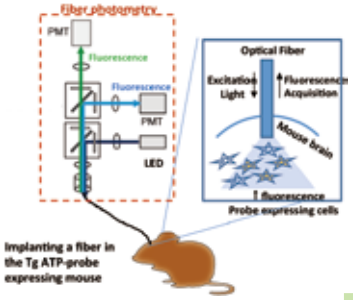
Taku Miyagawa

Understanding the genetic background and mechanism of sleep disorders.



Akiyo Natsubori

Understanding the brain metabolic dynamics of mice under sleep and wakefulness.



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