Nakanishi M, Niimura J, Yamasaki S, and Nishida A. (2017) "Death of dementia inpatients in Japanese psychiatric hospitals accounts for one-fifth of discharge destination in national data from 1996 to 2014" ***J. Alzheimers Dis.*** 56, 817-824.

Ando S, Koike S, Shimodera S, Fujito R, Sawada K, Terao T, Furukawa TA, Sasaki T, Inoue S, Asukai N, Okazaki Y, and Nishida A. (2017) "Lithium levels in tap water and the mental health problems of adolescents: an individual level cross-sectional survey." ***J. Clin. Psychiatry.*** 78(3):e252-e256.

Nakanishi M, Nakashima T, Shindo Y, Niimura J, and Nishida A. (2016) "Japanese care location and medical procedures for people with dementia in the last month of life." ***J. Alzheimers Dis.*** 51, 747-755

Yamasaki S, Ando S, Koike S, Usami S, Endo K, French P, Sasaki T, Furukawa TA, Hasegawa-Hiraiwa M, Kasai K, and Nishida A. (2016) "Dissociation mediates the relationship between peer victimization and hallucinatory experiences among early adolescents." ***Schizophr. Res. Cogn.*** 4, 18–23

Project Leader **Atsushi Nishida** Mental Health Promotion Project

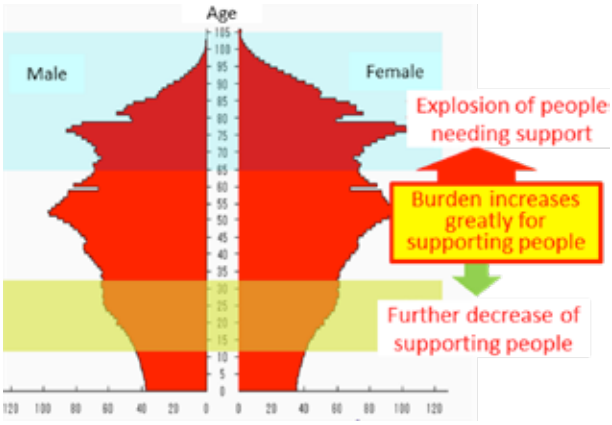
No health without Mental Health:

Mental Health promotion as the first priority in our society

While life in big cities, microcosms of today's stressful societies, is a full of risk factors for mental health, interpersonal bonds that support individuals are increasingly weakening. Hence, multifaceted research of mental health promotion via clinical medicine and sociomedical methodologies needs to be promoted.
The Mental Health Promotion Project engages in promoting mental well-being in big cities through, empirical findings from large-scale birth cohort studies conducted in partnership with municipalities in Tokyo which are experiencing increasingly aging populations and low birthrates, and developing programs in collaboration with clinical care units.

"We are trying to elucidate preventive factors for mental health problems and enhancing factors for mental well-being, and improve care for people living in communities and their families."

Our goals are as follows, 1) Elucidate preventive factors for mental health problems and enhancing factors for mental well-being in adolescence. 2) Improve care for people with dementia living in communities and their families, 3) Develop transition support programs connecting acute-phase hospital treatment and post-discharge outpatient treatment.



- **Increase in people with dementia:** Est. number in 2025 is 7 million (MHLW, 2014)
- The largest cause of health damage among **young people** is **mental illness and suicide** (Patton, Lancet, 2009)

Mental Health Promotion

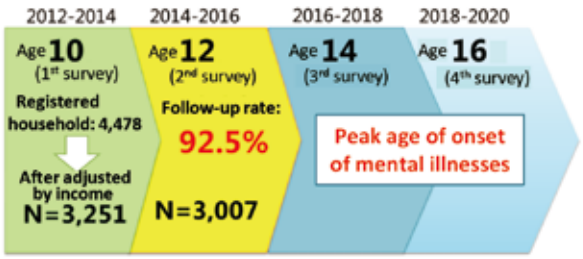
What we do

Elucidating contributing factors to adolescent mental health

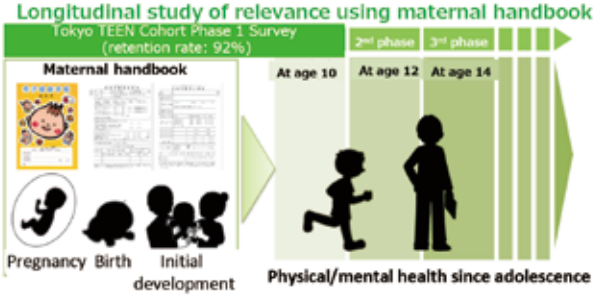
In adolescence, body and mind change significantly. Adolescents, therefore, are vulnerable to mental problems. Adolescent Health/Development Survey is a large-scale longitudinal birth cohort study included 10-year-old children and their carers living in Setagaya-ward, Chofu-city, and Mitaka-city. Currently, the study has completed the follow-up of children at their age 12; the follow-up rate is as high as 92.5%. The longitudinal relevance between the initial development at birth/childhood and the physical/mental health status since adolescence is also being studied based on information collected from maternal handbooks and various other health records.

[Adolescent Health/Development Survey]
TEEN COHORT

Progress of Health Development Survey (2017)

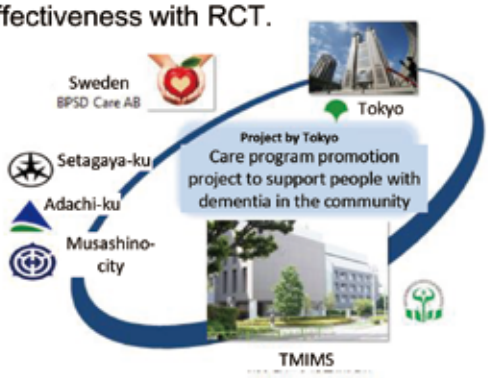


Longitudinal study of relevance using maternal handbook



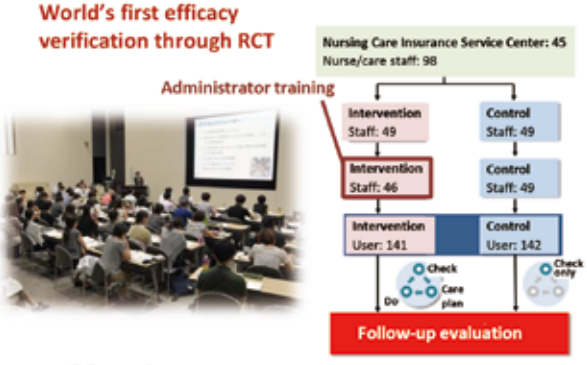
Care model development to support people with dementia at home

To support people with dementia living at home, it is indispensable to care Behavioral and Psychological Symptoms of Dementia (BPSD) as it is experienced by 90% of them. Being commissioned by Tokyo, we are working on to introduce highly-appreciated BPSD Care Program from Sweden. We aim to contribute to the dementia-related policies in Tokyo and improve the quality of dementia care through scientific verification of effectiveness with RCT.



Introduction of Sweden BPSD Care Program

World's first efficacy verification through RCT



Members

Atsushi Nishida
Syudo Yamasaki
Miharu Nakanishi
Junko Niimura
Kaori Endo
Kayo Hirooka
Yudai Iijima
Yu Yamamoto

Mental Health Promotion

Itokawa M, Miyashita M, Arai M, Dan T, Takahashi K, Tokunaga T, Ishimoto K, Toriumi K, Ichikawa T, Horiuchi Y, Kobori A, Usami S, Yoshikawa T, Amano N, Washizuka S, Okazaki Y, and Miyata T. (2018) "Pyridoxamine: A novel treatment for schizophrenia with enhanced carbonyl stress." ***Psychiatry Clin. Neurosci.*** 72: 35-44.

Miyashita M, Watanabe T, Ichikawa T, Toriumi K, Horiuchi Y, Kobori A, Kushima I, Hashimoto R, Fukumoto M, Koike S, Ujike H, Arinami T, Tatebayashi Y, Kasai K, Takeda M, Ozaki N, Okazaki Y, Yoshikawa T, Amano N, Washizuka S, Yamamoto H, Miyata T, Itokawa M, Yamamoto Y, and Arai M. (2016) "The regulation of soluble receptor for AGEs contributes to carbonyl stress in schizophrenia." ***Biochem. Biophys. Res. Commun.*** 479: 447-452.

Arai M, Miyashita M, Kobori A, Toriumi K, Horiuchi Y, Hatakeyama S, and Itokawa M. (2014) "Carbonyl stress and schizophrenia." ***Psychiatry Clin. Neurosci.*** 68: 655-665.

Miyashita M, Arai M, Kobori A, Ichikawa T, Toriumi K, Niizato K, Oshima K, Okazaki Y, Yoshikawa T, Amano N, Miyata T, and Itokawa M. (2014) "Clinical Features of Schizophrenia With Enhanced Carbonyl Stress." ***Schizophr. Bull.*** 40: 1040-1046.

Arai M, Nihonmatsu-Kikuchi N, Itokawa M, Rabbani N, and Thornalley PJ. (2014) "Measurement of glyoxalase activities." ***Biochem Soc. Trans.*** 42: 491-494.

Miyashita M, Arai M, Yuzawa H, Niizato K, Oshima K, Kushima I, Hashimoto R, Fukumoto M, Koike S, Toyota T, Ujike H, Arinami T, Kasai K, Takeda M, Ozaki N, Okazaki Y, Yoshikawa T, Amano N, Miyata T, and Itokawa M. (2014) "Replication of enhanced carbonyl stress in a subpopulation of schizophrenia." ***Psychiatry Clin. Neurosci.*** 68: 83-84.

Arai M, Koike S, Oshima N, Takizawa R, Araki T, Miyashita M, Nishida A, Miyata T, Kasai K, and Itokawa M. (2011) "Idiopathic carbonyl stress in a drug-naive case of at-risk mental state." ***Psychiatry Clin. Neurosci.*** 65: 606-607.

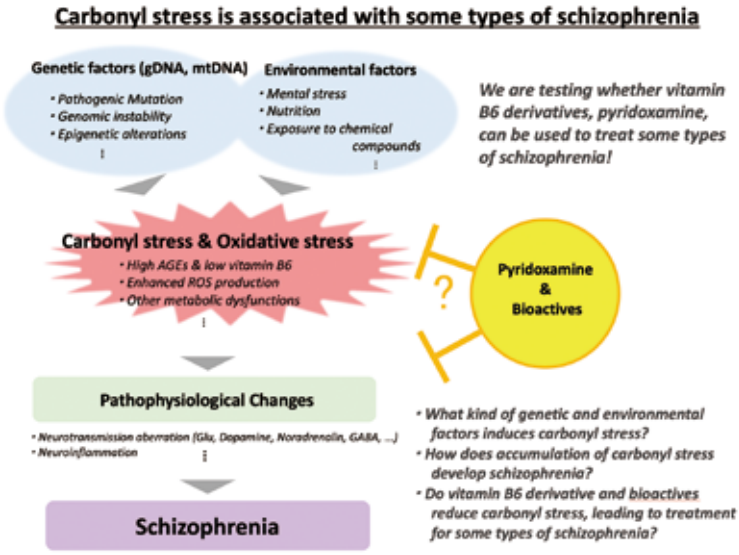
Arai M, Yuzawa H, Nohara I, Ohnishi T, Obata N, Iwayama Y, Haga S, Toyota T, Ujike H, Arai M, Ichikawa T, Nishida A, Tanaka Y, Furukawa A, Aikawa Y, Kuroda O, Niizato K, Izawa R, Nakamura K, Mori N, Matsuzawa D, Hashimoto K, Iyo M, Sora I, Matsushita M, Okazaki Y, Yoshikawa T, Miyata T, and Itokawa M. (2010) "Enhanced Carbonyl Stress in a Subpopulation of Schizophrenia." ***Arch. Gen. Psychiatry.*** 67: 589-597.

Project Leader **Makoto Arai** Schizophrenia Research Project

Identifying Biomarkers of Schizophrenia

Profiling of the peripheral metabolic system is a viable schizophrenia research strategy that can lead to earlier diagnostic methods, elucidation of molecular mechanisms, and novel strategies for the prevention and treatment of schizophrenia.
We focus on, 1) developing individualized medicine for treating schizophrenia, 2) investigating factors involved in disease onset, and 3) understanding the molecular pathology by using biomarkers to overcome the barrier of heterogeneity. Our research outcomes will be applied to drug development by establishing a new biomarker-based field of research in molecular psychiatry. Data obtained from metabolomics, genomics, induced pluripotent stem (iPS) cell models, animal models, post-mortem brain analyses, neuropsychology, and genetic counseling research will be consolidated to elucidate the genetic and environmental factors relevant to psychiatric disorders such as schizophrenia.

"Identifying biomarkers will allow us to classify schizophrenia into different types, and aid in earlier diagnoses and better treatments, leading to improvements in patients' quality of life."



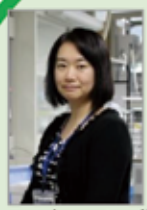
This biomarker-based approach is an innovative and creative strategy for identifying the metabolic changes associated with schizophrenia, independent of conventional pathological hypotheses. Verification in cellular and animal models can shed light on the molecular mechanisms underlying the utility of naturally-derived substances in trading schizophrenia, and is expected to lead to the future development of much safer treatments and prophylactic methods.

Schizophrenia Research

Topics of our research

- Clinical study
- Genomics
- Metabolomics
- Neuropsychology
- iPS cell models
- Mouse models
- Post-mortem brain analysis
- Genetic counseling

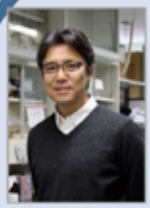
Yasue Horiuchi



Research of schizophrenia cell models and genetic counseling

Induced pluripotent stem cells (iPSCs) are believed to provide a powerful strategy to obtain and characterize central nervous system-relevant cells in vitro. We have successfully generated iPSCs, neurons and glial cells derived from patients with schizophrenia and carbonyl stress. We are confident such cellular models will supply us with a unique tool to study major mental disorders. Our other focus is making genetic counseling pervasive in the research and psychiatric field in Japan. (Please see our web site for more detail).

Mitsuhiro Miyashita



Investigating the pathophysiology and clinical relevance of schizophrenia with carbonyl stress.

We have found that carbonyl stress-related schizophrenia (SZ) presents a treatment-resistant phenotype. In our research, we try to elucidate the mechanism underlying how carbonyl stress affects onset and increases both hospitalization time and symptom severity in SZ, by investigating the elements of the AGEs-RAGE-inflammation axis. Additionally, we will examine longitudinally how carbonyl stress alters the clinical prognosis and physical complications in patients with SZ.

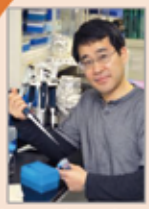
Our projects contribute to future innovation for preventive medical research in the areas of psychiatry, health, and welfare

Kazuya Toriumi

Development and analysis of mouse models based on schizophrenia pathophysiology

Based on clinical findings, we have developed genetic and/or environmental mouse models for schizophrenia, and analyzed them to uncover the molecular mechanisms underlying schizophrenia with carbonyl stress, oxidative stress and/or vitamin B6 deficiency. Moreover, using these mouse models, we have tried to explore new types of therapeutic drugs for schizophrenia that use different mechanisms of action than existing antipsychotics.

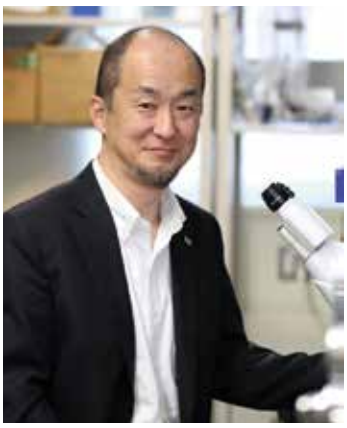
Masanari Itokawa



Clinical pharmacology of TM8001 in patients with carbonyl stress-related schizophrenia

TM8001 is a dihydrochloride of pyridoxamine, one of the vitamin B6 groups. TM8001 can act to capture reactive carbonyl compounds, and has inhibitory activity against the production of AGE by reactive carbonyl compounds. Thus, by reducing carbonyl stress, it is expected to be therapeutic in this type of schizophrenia. Removal of these substances is the key to a possible new treatment method based on the root cause of carbonyl stress-related schizophrenia.

Schizophrenia Research



Bauer M, (64 co-authors), Tatebayashi Y et al. (2014) "Relationship between sunlight and the age of onset of bipolar disorder: an international multisite study." ***J. Affect. Disord.*** 167:104-111.

Nihonmatsu-Kikuchi N, Hayashi Y, Yu XJ, and Tatebayashi Y. (2013) "Depression and Alzheimer's disease: novel postmortem brain studies reveal a possible common mechanism." ***J. Alzheimers Dis.*** 37: 11-21.

Tatebayashi Y, Nihonmatsu-Kikuchi N, Hayashi Y, Yu XJ, Soma M, and Ikeda K. (2012) "Abnormal fatty acid composition in the frontopolar cortex of patients with affective disorders." ***Transl. Psychiatry*** 2:e204.

Hayashi Y, Nihonmatsu-Kikuchi N, Hisanaga S, Yu XJ, and Tatebayashi Y. (2012) "Neuropathological similarities and differences between schizophrenia and bipolar disorder: a flow cytometric postmortem brain study." ***PLoS One.*** 7: e33019.

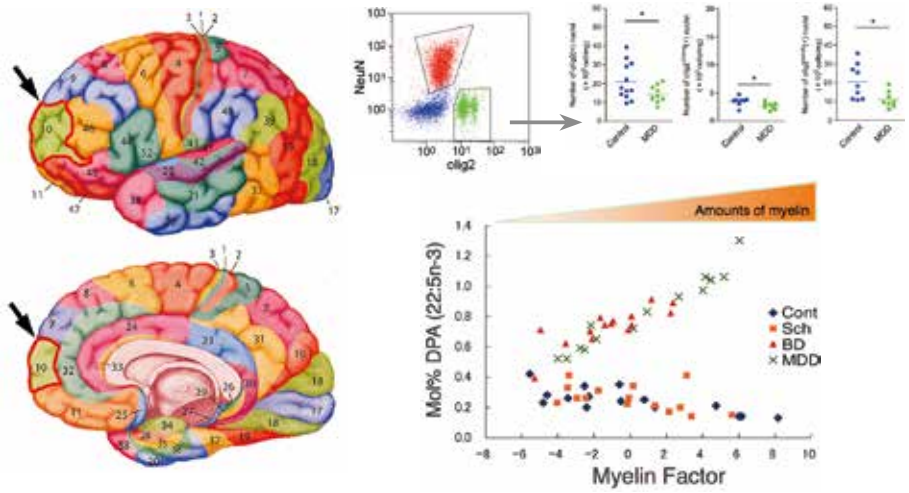
Hayashi Y, Nihonmatsu-Kikuchi N, Yu XJ, Ishimoto K, Hisanaga SI, and Tatebayashi Y. (2011) "A novel, rapid, quantitative cell-counting method reveals oligodendroglial reduction in the frontopolar cortex in major depressive disorder." ***Mol. Psychiatry.*** 16: 1155-1158.

Project Leader **Yoshitaka Tatebayashi** Affective Disorders Research Project

Our Goal is to Decipher the Neurobiological Bases of Affective Disorders.

Major depressive disorder (MDD) and bipolar disorder (BD), collectively known as affective disorders, are relapsing and remitting disorders of affect with nearly full recovery between episodes. We use human postmortem brains and animal and cell culture models to identify the processes in which stress or aging causes changes in brain to induce these disorders. A major focus of our work is stress-induced or age-related changes in cellular structure, especially that of oligodendrocyte lineage cells and lipids, within the brain's mood circuitry. We are also interested in the biological relationship between affective disorders and dementias such as Alzheimer's disease.

"Our human postmortem brain studies reveal oligodendroglial reductions and myelin-dependent fatty acid abnormalities in the frontopolar cortex in affective disorders."



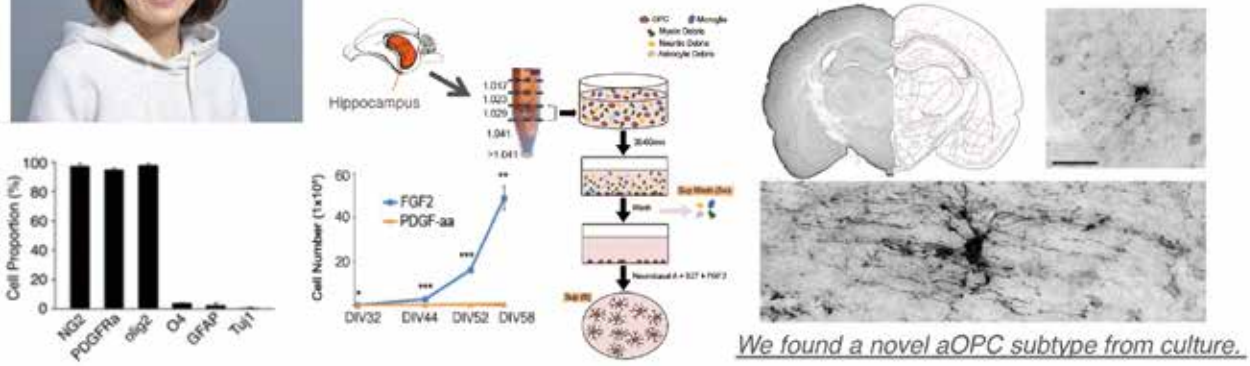
The exact functions of the human frontopolar cortex (BA10) remain enigmatic. Given that the BA10 is thought to be the most evolutionarily recent expansion of the primate prefrontal cortex, its function may uniquely reflect human adaptations in the context of selecting and updating models of reward contingency in dynamic environments. As adulthood cortical myelination is an essential process for the establishment of efficient neuronal signaling networks, any abnormalities in this process may have important roles in the pathophysiology of affective disorders.

Affective Disorders Research

"Better understanding of these phenomena will provide important insights to facilitate the more effective diagnosis, treatment and prevention of affective disorders."

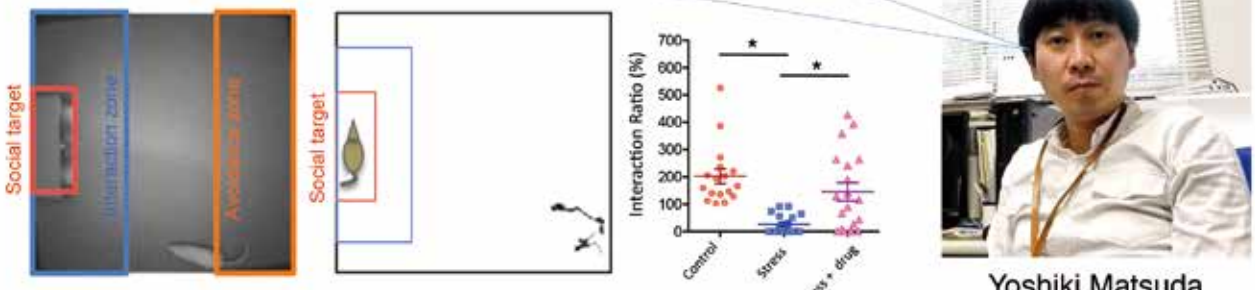
Naomi Nihonmatsu-Kikuchi

We purify and culture adult oligodendrocyte progenitor cells (aOPCs) from adult mammalian brains to understand their roles in the pathogenesis of affective disorders.



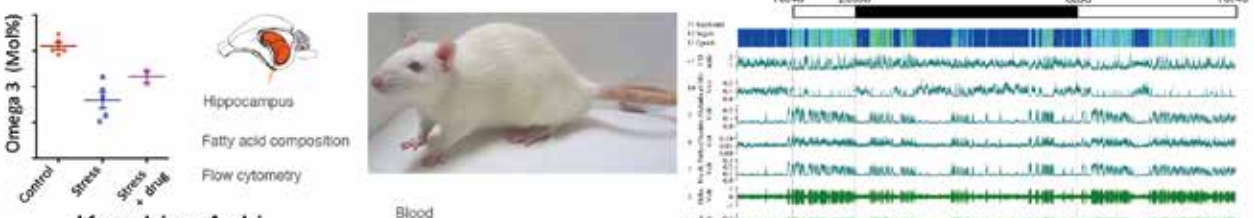
We found a novel aOPC subtype from culture.

Our animal model clearly indicates essential roles of inflammation in the pathophysiology of depression. Chronic stress induces changes not only in behavior but also in electrophysiology and cellular structure.



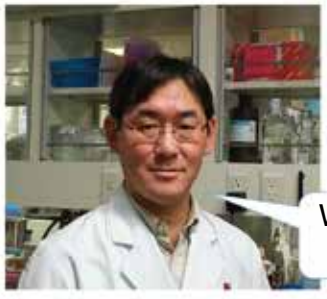
Yoshiki Matsuda

We found a therapeutic effect of anti-inflammatory drugs.



Kazuhisa Aoki

We found several candidate blood biomarkers for psychosocial stress.



We are conducting detailed "omics" analyses of our animal models to discover novel biomarkers for depression.

Affective Disorders Research

Shimada M, Miyagawa T, Toyoda H, Tokunaga K, and Honda M. (2018) "Epigenome-wide association study of DNA methylation in narcolepsy: an integrated genetic and epigenetic approach." ***Sleep*** 41:zsy019

Toyoda H, et al. (2017) "Narcolepsy susceptibility gene CCR3 modulates sleep-wake patterns in mice." ***PLoS ONE*** 12:e0187888

Miyata R, Hayashi M, Kohyama J, and Honda M.(2017) "Steroid therapy ameliorated cataplexy in three children with recent-onset of narcolepsy." ***Sleep Med.*** 29:86-87.

Tanaka S, Honda Y, Honda M, Yamada H, Honda K, and Kodama T. (2017) "Anti-tribbles pseudokinase 2 (TRIB2)-immunization modulate Hypocretin/Orexin neuronal functions." ***Sleep*** 40:zsw036.

Miyagawa T, et al. (2015) "New susceptibility variants to narcolepsy identified in HLA class II region." ***Hum. Mol. Genet.*** 24:891-898.

Miyagawa T, et al. (2013) "Effects of oral L- carnitine administration in narcolepsy patients: a randomized, double-blind, cross-over and placebo-controlled trial." ***PLoS ONE*** 8:e53707.

Miyagawa T, et al. (2011) "Abnormally low serum acylcarnitine levels in narcolepsy patients." ***Sleep*** 34:349-353.

Tanaka S, Honda M (2010) "IgG abnormality in narcolepsy and idiopathic hypersomnia." ***PLoS ONE*** 5: e955.

Toyoda H, et al. (2010) "Anti-tribbles homolog 2 autoantibodies in Japanese patients with narcolepsy." ***Sleep*** 33:875-878.

Honda M, et al. (2009) "IGFBP3 colocalizes with and regulates hypocretin(orexin)." ***PLoS ONE*** 4:e4254.

Honda M, Arai T, et al. (2009) "Absence of ubiquitinated inclusions in hypocretin neurons of narcolepsy patients." ***Neurology*** 73:511-517.

Tanaka S, Honda Y, Inoue Y, and Honda M. (2006) "Detection of autoantibodies against hypocretin, hcrtr1, and hcrtr2 in narcolepsy: anti-Hcrt system antibody in narcolepsy." ***Sleep*** 29:633-638.

Project Leader **Makoto Honda** Sleep Disorders Project

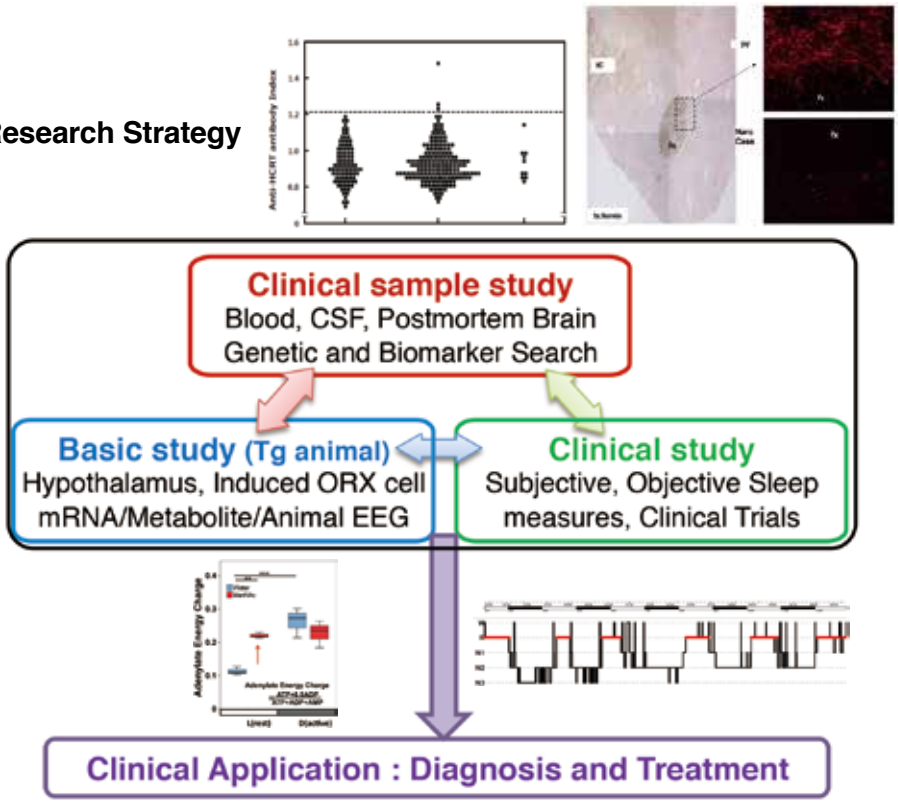
Narcolepsy and Hypersomnia:
Find the causes to develop better treatments

Narcolepsy is a sleep disorder of 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 the 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

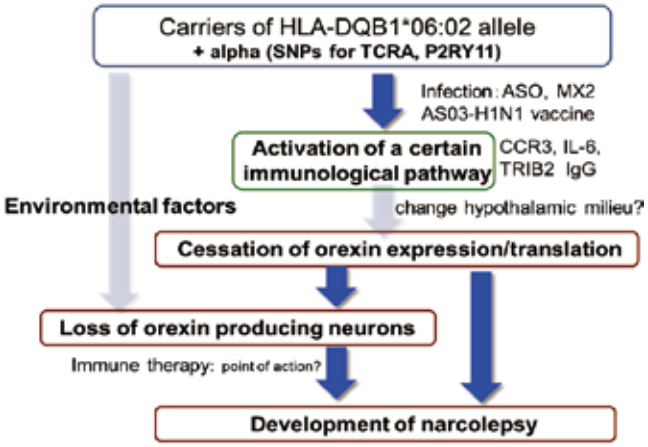


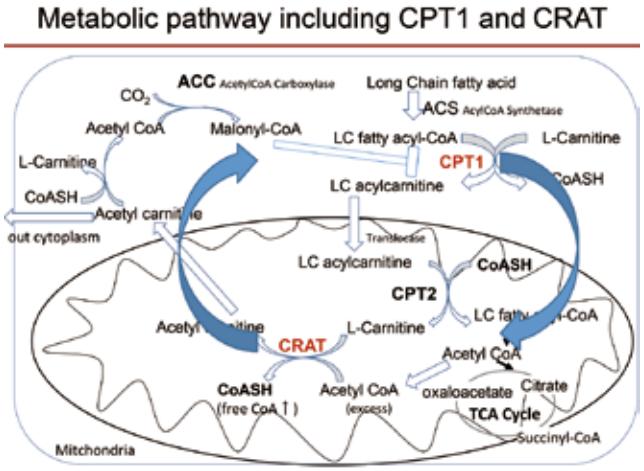
Research Interests

The hypothalamus works as a center for sleep-wake switching and integrates information from the body for this process. We are particularly interested in how the body's immune and metabolic status affect sleep. This may be a key to understanding altered sleep-wake regulation in narcolepsy.

1. HLA association and immune abnormality

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





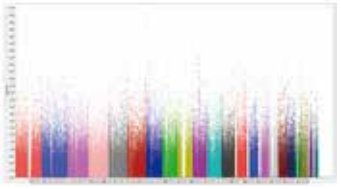
2. Metabolic aspect of narcolepsy and related hypersomnia

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

Members of Sleep Disorders Project (2017)

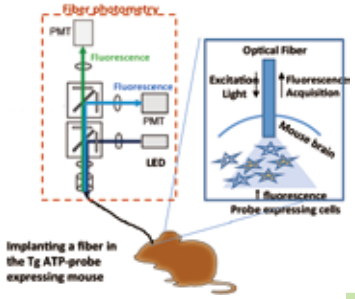
Taku Miyagawa

Understanding the genetic background and mechanism of sleep disorders.



Akiyo Natsubori

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



Sleep Disorders

Project Leader **Kazutaka Ikeda** Addictive Substance Project

Addictive Drugs are Double-edged Sword: They can be both harmful and beneficial, depending on how they are used

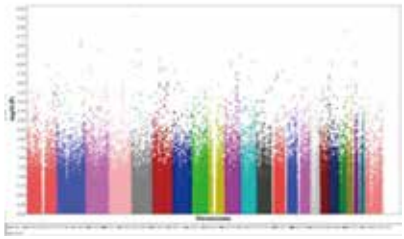
Addiction to various substances (e.g., drugs, alcohol, and tobacco) and behaviors (e.g., Internet and gambling) is a serious public health problem. The use of legal drugs has been increasing in Japan in recent years. Thus, preventing and solving problems that are related to addiction are important.

Some addictive drugs are also widely used as analgesics and for the treatment of developmental disorders. Some molecules that are involved in the actions of addictive drugs may be shared between analgesia and developmental disorders.

The goals of our project are the following: (1) developing novel treatments for addiction and prevention, (2) improving personalized pain treatment, and (3) developing novel treatments for developmental disorders.

"We are trying to improve treatment, prevention, and our understanding of addiction, pain, and developmental disorders by revealing the mechanisms that underlie addiction."

Attaining these goals will make significant contributions to society. We seek to accomplish these goals by studying the actions of addictive drugs using molecular biological, behavioral pharmacological, human genomic, and clinical approaches.



Kotajima-Murakami H, Kobayashi T, Kashii H, Sato A, Hagino Y, Tanaka M, Nishito Y, Takamatsu Y, Uchino S, Ikeda K. (2018) "Effects of rapamycin on social interaction deficits and gene expression in mice exposed to valproic acid in utero." ***Mol. Brain*** 12:3

Sugaya N, Ogai Y, Aikawa Y, Yumoto Y, Takahama M, Tanaka M, Haraguchi A, Umeno M, and Ikeda K. (2018) "A randomized controlled study of the effect of ifenprodil on alcohol use in patients with alcohol dependence." ***Neuropsychopharmacology Rep***.38(1):9-17.

Ide S, Ikeda K. (2018) "Mechanisms of the antidepressant effects of ketamine enantiomers and their metabolites. " ***Biol. Psychiatry.*** 84:551-552.

Fujita M, Hagino Y, Takeda T, Kasai S, Tanaka M, Takamatsu Y, Kobayashi K, and Ikeda K. (2017) "Light/dark phasedependent spontaneous activity is maintained in dopamine-deficient mice." ***Mol. Brain.*** 10: 49.

Nishizawa D, Fukuda K, Kasai S, Hasegawa J, Aoki Y, Nishi A, Saita N, Koukita Y, Nagashima M, Katoh R, Satoh Y, Tagami M, Higuchi S, Ujike H, Ozaki N, Inada T, Iwata N, Sora I, Iyo M, Kondo N, Won MJ, Naruse N, Uehara K, Itokawa M, Koga M, Arinami T, Kaneko Y, Hayashida M, and Ikeda K. (2014) "Genome-wide association study identifies a potent locus associated with human opioid sensitivity." ***Mol. Psychiatry.*** 19: 55-62.

Sato A, Kasai S, Kobayashi T, Takamatsu Y, Hino O, Ikeda K, and Mizuguchi M. (2012) "Rapamycin reverses impaired social interaction in mouse models of tuberous sclerosis complex" ***Nat. Commun.*** 3: 1292.

Addictive Substance

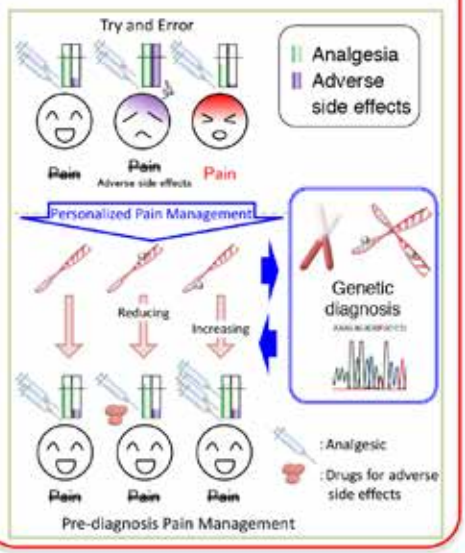
Topics of our research

Addiction research

We study the mechanisms of action of opioids, dopamine, and hallucinogens (e.g., phencyclidine) to reveal the etiology of addiction using several mouse models and behavioral pharmacological approaches. In parallel with basic research, we are also developing a clinical scale to measure addiction severity.

Pain treatment research

The sensitivity to opioid analgesics is associated with polymorphisms of several genes. Based on genomic information, we are developing personalized pain treatments.



Developmental disorder research

We focus on autism and attention-deficit/ hyperactivity disorder (ADHD). Tuberous sclerosis complex 1 and 2 heterozygous knockout mice and dopamine transporter knockout mice are mainly used as models of autism and ADHD, respectively. We seek to develop novel treatments for autism.

Members

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