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.

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 of Tokyo which is experiencing increasingly aging population and low birthrate; and developing programs in collaboration with clinical forefront of care.

“No health without Mental Health: Mental Health promotion as the first priority in our society”

Our goals are as follows: 1) Elucidate preventive factors to mental health problems and enhancing factors to mental well-being, and to improve care for people living in the community and their families.

No health without Mental Health:
Mental Health promotion as the first priority in our society

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

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

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

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

Administrator training

Longitudinal study of relevance using maternal handbook

Follow-up evaluation

Members

Atsushi Nishida
Syudo Yamasaki
Miharu Nakanishi
Junko Niimura
Kaori Endo
Kayo Hirooka
Yudai Iijima
Yu Yamamoto
The profiling of the peripheral metabolic system is a viable schizophrenia research strategy that can lead to earlier diagnostic methods, elucidation of its molecular mechanisms, and novel strategies for the prevention and treatment.

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 anticipated to become an innovative and creative strategy for elucidating the metabolic system of schizophrenia disease expression independently of conventional pathological hypotheses. Verification in cellular and animal models can shed light on the molecular mechanisms underlying the utility of naturally-derived substances, and is expected to lead to the future development of much safer treatments and prophylactic methods.
Topics of our research

- Clinical study
- Genomics
- Metabolomics
- Neuropsychology

- iPS cell models
- Mouse models
- Post-mortem brain analysis
- Genetic counseling

Yasue Horinuchi
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).

Mitsuhito 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 axes. Additionally, we will examine longitudinally how carbonyl stress alters the clinical prognosis and physical complications in patients with SZ.

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.

Masanori Itohara
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.

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

Schizophrenia Research
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.
“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.

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 novel aOPC subtype from culture.

We found a therapeutic effect of anti-inflammatory drugs.

Kazuhisa Acki

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

We found several candidate blood biomarkers for psychosocial stress.
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 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.

Taku Miyagawa
Understanding the genetic background and mechanism of sleep disorders.

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

Members of Sleep Disorders Project (2017)
Addiction to substances (e.g. drugs, alcohol, tobacco) and behavior (e.g. internet, gambling) is a serious public health problem. Moreover, use of legal drugs has been increasing in Japan in recent years. It is important to prevent and solve problems of addictions.

On the other hand, some addictive drugs are also widely used as analgesics and treatment of developmental disorders. Thus, it is considered that some molecules involved in action of addictive drugs are commonly related to analgesics and developmental disorders.

The goals of our project are as follows: 1) Development of novel treatment and prevention of addiction. 2) Improvement of personalized pain treatment. 3) Development of novel treatment against developmental disorders.

“We are trying to improve treatment, prevention, and understanding of addiction, pain, and developmental disorders by revealing the mechanisms underlying addiction.”

All goals can make significant contribution to the society. We aim to those goals through studying the action mechanisms of addictive drugs using molecular biological approach, behavioral pharmacological approach, human genome analysis, and clinical approach.
**Addiction research**
We study action mechanisms of opioids, dopamine, and hallucinogens such as phencyclidine to reveal the onset of addiction using several mouse models and behavioral pharmacological study. In parallel with the basic research, we also develop and verify a scale for addiction severity.

**Pain treatment research**
Sensitivity of opioid analgesics is associated with polymorphisms of several genes. Based on the genome information, we develop personalized pain treatment.

**Developmental disorder research**
We focus on autism and attention deficit hyperactivity disorder (ADHD). In our project, tuberous sclerosis complex 1 and 2 hetero knockout mouse and dopamine transporter knockout mouse are mainly used as models of autism and ADHD, respectively. We are finding novel treatments for autism.

**Members**
Kazutaka Ikeda
Shinya Kasai
Daisuke Nishizawa
Soichiro Ide
Sei Ohka
Masayo Fujita
Hiroko Kotajima