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.

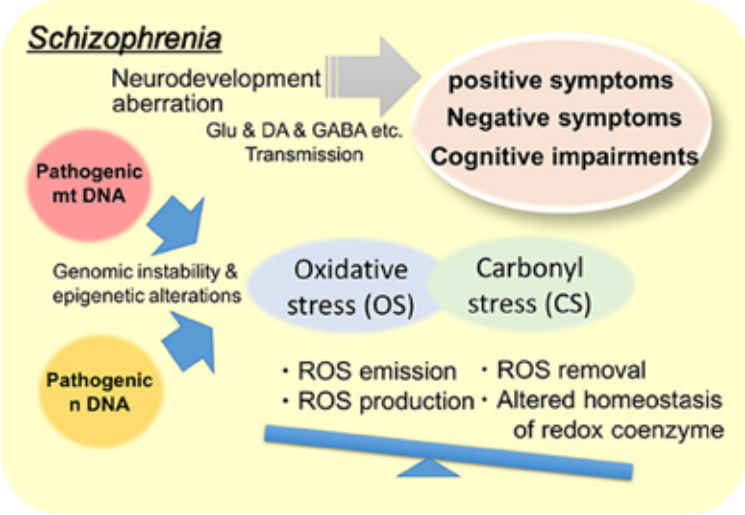
Arai M, Yuzawa H, Nohara I, Ohnishi T, Obata N, Iwayama Y, Haga S, Toyota T, Ujike H, Arai M, Ichikawa T, Nishida A, Tanaka Y, Furukawa A, Aikawa Y, Kuroda O, Niizato K, Izawa R, Nakamura K, Mori N, Matsuzawa D, Hashimoto K, Iyo M, Sora I, Matsushita M, Okazaki Y, Yoshikawa T, Miyata T, and Itokawa M. (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

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."



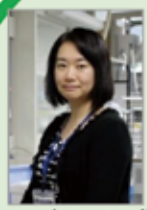
This biomarker-based approach is anticipated to become an innovative and creative strategy for elucidating the metabolic system of schizophrenia disease expression independently of conventional pathological hypotheses. Verification in cellular and animal models can shed light on the molecular mechanisms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

Schizophrenia Research

Topics of our research

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

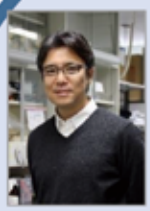
Yasue Horiuchi



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.

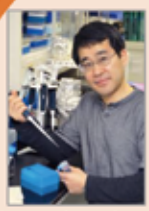
Our projects contribute to future innovation for preventive medical research in the areas of psychiatry, health, and welfare

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