1. Introduction
Schizophrenia, a chronic, severe, and disabling brain disorder, is thought to be a heterogeneous syndrome with a prevalence of approximately 1% worldwide. This disease is characterized by positive and negative symptoms that can influence thoughts, perceptions, speech, affect and behaviors. Several lines of evidence from family, twin and adoption studies suggest the contribution of genetic factors, environments, psychological and social processes to develop this illness. From molecular genetics and cytogenetic studies, potential candidate genes and chromosomal linkage loci for schizophrenia have been identified. Genetic studies of schizophrenia, however, have generally been disappointing, since the data obtained often cannot be reproduced. Heterogeneity in schizophrenia makes the search for molecular mechanisms much more difficult.

2. Carbonyl stress as biomarker of schizophrenia?
Several studies support the importance that early intervention is associated with a more favorable outcomes such as course of illness and reduced duration of hospitalization in patients with schizophrenia. Accumulation of toxic reactive carbonyl compounds, which referred to as carbonyl stress, results in the modification of proteins and the eventual formation of advanced glycation end products such as pentosidine. Cellular removal of carbonyl compounds hinges largely upon the activity of glyoxalase I (Glo1). We previously reported that approximately 17% of patients with schizophrenia exhibit carbonyl stresses with high plasma pentosidine levels and depletion of serum vitamin B6 in spite of no physical complications. Of those psychiatric patients with carbonyl stress, we also found several schizophrenia having novel heterozygous frameshift mutations in Glo1 gene with 40-50% reduction of enzymatic activity and homozygous of missense mutation in the gene concomitant with 15-20% less active Glo1. These results suggest that pentosidine accumulation and vitamin B6 depletion were involved in pathophysiology of schizophrenia in those patients since cases carrying genetic Glo1 deficit could suffer from the stress before onset of the disease.

3. Strategy to inhibit carbonyl stress
Specific biomarkers for schizophrenia have the potential to be useful for identifying patients at risk of developing the disease and distinguish biologically meaningful subgroups within the disease. Plasma pentosidine level is significantly low in outpatients than that of hospitalized cases, positive and negative syndrome scale (PANSS) is significantly correlated with plasma
levels of pentosidine, and a follow-up study showed decrease of pentosidine levels accompanied with improvement of psychotic symptoms that are less sever PANSS after follow-up compared to that of beginning of the observation. Recently, we reported on a drug-naive patient with at-risk mental state, who exhibited enhanced carbonyl stress with high plasma pentosidine levels, suggesting the possibility that the stress could exist before onset of the disease. These findings support that carbonyl stress characterizes the psychosis risk state for at least a subset of patients with schizophrenia, and that pentosidine would be a hopeful biomarker of schizophrenia and developing new therapeutic technologies for the disease.

Clinical characteristics of schizophrenia with carbonyl stress suggested that improvement of the stress is a new therapeutic way of psychiatric disorders. Agents able to inhibit AGEs formation or entrap carbonyl compounds may also prove to be of therapeutic value, if carbonyl stress is directly linked to schizophrenic signs and symptoms. We regard pyridoxamine, a non-toxic, water-soluble vitamin B6, as a novel medicine for schizophrenia with carbonyl stress because it inhibits the formation of AGEs.

4. Conclusions

Carbonyl stress is a new target of medication for schizophrenia without neurotransmitter based concept of therapeutics and inhibiting the carbonyl stress by pyridoxamine is expected to cure negative symptoms and treatment-registrant cases using conventional medications. In particular, the markedly high pentosidine level in schizophrenic patients with low vitamin B6 level suggest that pyridoxamine may prove clinical useful. Further studies are needed to verify the effect of antipsychotic medication on elevated plasma pentosidine and characterize clinical features of schizophrenia with carbonyl stress as well as elucidating precise molecular mechanisms of pentosidine in central nerve systems of the disease.

In my talk, I would like to provide a brief overview of omics-based medicine of the disease, and in vivo phase II clinical trial using pyridoxamine and in vitro biological study in progress will be discussed during the session.

References
