

Astellas and Fujita Health University Discover Neuronal Maturation Deficits in Patients Suffering from Schizophrenia and Bipolar Disorder

~Data Reported in U.S. Scientific Journal, Translational Psychiatry~

TOKYO, July 25, 2012 - [Astellas Pharma Inc.](#) (“Astellas”; Tokyo:4503; President and CEO: Yoshihiko Hatanaka) and Fujita Health University (Aichi, President: Yoshikazu Kurosawa) announced that Astellas Research Institute of America LLC (ARIA), in collaboration with Dr. Tsuyoshi Miyakawa at Institute for Comprehensive Medical Science, Fujita Health University and Stanley Medical Research Institute (SMRI), has discovered deficits in maturation steps of neurogenesis within the hippocampus of patients with schizophrenia / bipolar disorder. This discovery was reported in a Scientific Journal called Translational Psychiatry on July 10, 2012.

The hippocampus is a brain structure that plays a primary role of learning and memory and also controls emotion and stress responses. Previous studies have found strong links between hippocampal malfunction and psychiatric disorders, including schizophrenia and bipolar disorder. The hippocampus is also known as one of the only two brain regions that have new neurons generated into adulthood (adult neurogenesis). It is believed that the disturbances in the generation of new neurons may affect the function of the hippocampus, resulting in behavioral and cognitive alterations seen in some psychiatric diseases.

Human genetics studies have discovered that genetic variations (mutations) constitute predisposition to schizophrenia and bipolar disorder. Dr. Miyakawa’s research group at Fujita Health University reported that a subgroup of gene-manipulated mouse mutants show not only behavioral deficits reminiscent of patients with psychiatric disorders (including cognitive deficits and social withdrawal) but also deficits in maturation of newly-born neurons in the hippocampus. Specifically, mutant mice have more immature neurons (expressing protein marker Calretinin) and less mature neurons (expressing protein marker Calbindin) in their hippocampal dentate gyrus, resulting in alternations of neuronal electrophysiological properties and malfunction of hippocampal neural circuit. This phenomena, referred to as an “immature dentate gyrus” (iDG), may underlie behavioral deficits observed in these mutants.

Building on the findings of the Miyakawa group, scientists at ARIA have examined the hippocampi from four groups (schizophrenia, bipolar disorder, depression and healthy control) of postmortem brain for the hallmarks of iDG. They discovered that the immature neuronal marker Calretinin was significantly increased in both schizophrenia and bipolar disorder groups and mature neuronal marker Calbindin show a trend toward decrease in bipolar disorder patients. Calretinin expression levels were positively correlated

with patients' clinical data, namely, presence of psychosis and suicide as a cause of death. These findings suggest a possibility that drugs that ameliorate this iDG phenotypes may become a truly innovative approach to cure psychiatric disorders, such as schizophrenia and bipolar disorder.

Astellas and Fujita Health University expect to unveil the mechanisms of brain diseases and identify innovative pharmaceuticals by proceeding this study for neuronal maturation deficits in the hippocampus.

<Reference>

The title and authors of the article reported in Translational Psychiatry published on July 10, 2012 (local time) are as follows:

Title : Detection of an immature dentate gyrus feature in human schizophrenia/bipolar patients
Authors : NM Walton, Y Zhou, JH Kogan, R Shin, M Webster, AK Gross, CL Heusner, Q Chen, S Miyake, K Tajinda, K Tamura, T Miyakawa and M Matsumoto

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About Astellas Pharma Inc.

Astellas Pharma Inc. was created from the merger of Yamanouchi Pharmaceutical Co., Ltd. and Fujisawa Pharmaceutical Co., Ltd. in April 2005 and is a global pharmaceutical company with ethical pharmaceuticals as its core business. Astellas has already established its position as the world's leading company in the fields of urology and transplantation. Moving forward, Astellas has identified urology, immunology (including transplantation) and infectious diseases, oncology, neuroscience, and DM complication and kidney diseases as five focused areas of research for the company, and is promoting research to develop revolutionary new drugs that are needed for the treatment of diseases in these five areas. In order to continually create promising discovery projects and enrich the research pipeline, close collaborative research will be aggressively pursued with leading edge research institutions in addition to promotion of Astellas research.

About Astellas Research Institute of America LLC

Astellas Research Institute of America LLC ("ARIA") is one of Astellas' research facilities outside Japan. ARIA focuses on next generation drug discovery and research in the fields of immunology and neuroscience. In the process of drug discovery, translational research bridging non-clinical (animal model studies) and clinical (human patient studies) is critical. To strengthen translational research in psychiatry drug discovery, ARIA has commenced a research collaboration with the Lieber Institute for Brain Development (<http://www.libd.org/>) to conduct comparative gene expression analysis in brains from gene-manipulated mouse mutant models and schizophrenia / bipolar disorder patients. The ultimate goal of this collaborative research is to spur the development of truly innovative treatment for patients suffering from severe lifelong psychiatric disorders.

About Fujita Health University

Fujita Health University was founded as a medical school by Prof. Keisuke Fujita, M.D., Ph.D., in September 1964. Located in Japan's Aichi Prefecture, the school is comprised of a graduate school of medicine and health sciences, a school of medicine, a school of medical science, and a school of health sciences that includes a nursing program. Since its establishment the university has produced a great number of talented doctors, nurses and medical technologists. In 1985, Prof. Fujita established the molecular medicine section inside the Institute of Comprehensive Medical Science, where he analyzed various intractable diseases at a molecular level and developed leading-edge treatments. The university's mission is to contribute to society through education of the best medical professionals and the provision of advanced medical development based on the philosophy of "Dokusou-Ichiri - The Principle of Originality," which Prof. Fujita advocated.

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