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STEM CELL RESEARCH IDENTIFIES NEW GENE TARGETS IN PATIENTS WITH EARLY-ONSET ALZHEIMER'S DISEASE

Scientists provide new insight into cause of Alzheimer's disease

NEW YORK, NY (January 8, 2014) – Scientists at The New York Stem Cell Foundation (NYSCF) Research Institute in collaboration with scientists at the Icahn School of Medicine at Mount Sinai (ISMMS) successfully generated a stem cell model of familial Alzheimer's disease (FAD). Using this stem cell model, researchers identified fourteen genes that may be implicated in the disease and one gene in particular that shows the importance that inflammation may play in the brain of Alzheimer's patients.

In this study, published today in *PLOS ONE*, the team of scientists produced stem cells and neural precursor cells (NPCs), representing early neural progenitor cells that build the brain, from patients with severe early-onset AD with mutations in the Presenilin 1 (*PSEN1*) gene. These NPCs had elevated Abeta42/Abeta40 ratios, indicating elevation of the form of amyloid found in the brains of Alzheimer's patients. These levels were greater than those in adult cells that did not have the *PSEN1*mutation. This elevated ratio showed that these NPCs grown in the petri dish were accurately reflecting the cells in the brains of FAD patients.

"Our ability to accurately recapitulate the disease in the petri dish is an important advance for this disease. These genes provide us with new targets to help elucidate the cause of sporadic forms of the disease as well provide targets for the discovery of new drugs," said Susan L. Solomon, Chief Executive Officer of The New York Stem Cell Foundation.

"The gene expression profile from Noggle's familial Alzheimer's stem cells points to inflammation which is especially exciting because we would not usually associate inflammation with this particular Alzheimer's gene. The greatest breakthroughs come with 'unknown unknowns', that is, things that we don't know now and that we would never discover through standard logic," said Sam Gandy, MD, PhD, Professor of Neurology and Psychiatry and Director of the Center for Cognitive Health at the Icahn School of Medicine at Mount Sinai and a co-author on the study. Gandy is also Associate Director of the NIH-Designated Mount Sinai Alzheimer's Disease Research Center.

The researchers generated induced pluripotent stem (iPS) cells from affected and unaffected individuals from two families carrying *PSEN1* mutations. After thorough characterization of the NPCs through gene expression profiling and other methods, they identified fourteen genes that behaved differently in *PSEN1* NPCs relative to NPCs from individuals without the mutation. Five of these targets also showed differential expression in late onset Alzheimer's disease patients' brains. Therefore, in the *PSEN1* iPS cell model, the researchers reconstituted an essential feature in the molecular development of familial Alzheimer's disease.

Although the majority of Alzheimer's disease cases are late onset and likely result from a mixture of genetic predisposition and environmental factors, there are genetic forms of the disease that affect patients at much earlier ages. *PSEN1* mutations cause the most common form of inherited familial Alzheimer's disease and are one hundred percent penetrant, resulting in all individuals with this mutation getting the disease.

The identification of genes that behaved differently in patients with the mutation provides new targets to further study and better understand their effects on the development of Alzheimer's disease. One of these genes, NLRP2, is traditionally thought of as an inflammatory gene.

"The fact that the NLRP2 gene is upregulated in these cells is interesting because inflammatory genes have long been implicated in late onset and sporadic forms of the disease. The importance is still unknown, but these cells may provide a platform to understand the function of this gene as well as others that contribute to Alzheimer's disease," said Scott Noggle, PhD, NYSCF – Charles Evans Senior Research Fellow for Alzheimer's Disease and Director of the New York Stem Cell Foundation (NYSCF)'s laboratory and senior author on the study.

While other groups have recently generated human iPS cells models of Alzheimer's disease with studies primarily focused on familial Alzheimer's disease neurons, none of these studies addressed whether there are any differences between Alzheimer's disease and control neural progenitor cells prior to neuronal differentiation.

Studying neural progenitor cells may also reveal developmental components of familial Alzheimer's disease, and are more homogenous than the wide variety of neurons currently produced by differentiation protocols, which allows for better comparisons between controls and disease cells.

Dr. Gandy and Dr. Noggle are both members of the Cure Alzheimer's Stem Cell Consortium that supported this research. The Stem Cell Consortium is an international group of scientists that are working together to directly investigate, for the first time, the brain cells from individuals with the common form of Alzheimer's disease. Other members of the Consortium include Kevin Eggan, PhD, of Harvard University, Marc Tessier-Lavigne, PhD, of Rockefeller University, Doo Kim, PhD, of Harvard Medical School, and Tamir Ben-Hur, MD, PhD, of Hadassah University.

NYSCF stem cell researcher Andrew Sproul, PhD, a staff scientist at the NYSCF Research Institute is the lead author on this study. Samson Jacob of NYSCF, other NYSCF and

ISMMS researchers, scientists at Columbia University, and the James J. Peters VA Medical Center also made significant contributions to this study.

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About The New York Stem Cell Foundation

The New York Stem Cell Foundation (NYSCF) is an independent organization founded in 2005 to accelerate cures and better treatments for patients through stem cell research. NYSCF employs over 45 researchers at the NYSCF Research Institute, located in New York, and is an acknowledged world leader in stem cell research and in developing pioneering stem cell technologies, including the NYSCF Global Stem Cell Array™. Additionally, NYSCF supports another 60 researchers at other leading institutions worldwide through its Innovator Programs, including the NYSCF – Druckenmiller Fellowships and the NYSCF – Robertson Investigator Awards. NYSCF focuses on translational research in a model designed to overcome the barriers that slow discovery and replaces silos with collaboration.

NYSCF researchers have achieved six major discoveries in the field, including: the first stem cell-derived beta cell model that accurately reflects the features of a genetic form of diabetes in June 2013; the generation of functional, immune-matched bone substitutes from patients' skin cells (featured in *The Wall Street Journal* in May 2013); the discovery of a clinical cure to prevent transmission of maternally inherited mitochondrial diseases in December 2012; the derivation of the first-ever patient specific embryonic stem cell line (#1 Medical Breakthrough of 2011 by *Time* magazine); the discovery of a new way to reprogram stem cells; and, the creation of the first disease model from induced pluripotent stem cells (also named the #1 Medical Breakthrough by *Time* magazine in 2008). More information is available at www.nyscf.org.

About The Mount Sinai Medical Center

The Mount Sinai Medical Center encompasses both The Mount Sinai Hospital and Icahn School of Medicine at Mount Sinai. Established in 1968, the Icahn School of Medicine is one of the leading medical schools in the United States, with more than 3,400 faculty in 32 departments and 14 research institutes. It ranks among the top 20 medical schools both in National Institutes of Health (NIH) funding and by U.S. News & World Report. The Mount Sinai Hospital, founded in 1852, is a 1,171-bed tertiary- and quaternary-care teaching facility and one of the nation's oldest, largest and most-respected voluntary hospitals. The Mount Sinai Hospital is nationally ranked by U.S. News & World Report as one of the top 25 hospitals in 7 specialties based on reputation, safety, and other patient-care factors.