



Contact: David McKeon
212-365-7440
dmckeon@nyscf.org

SCIENTISTS CREATE PARKINSON'S DISEASE IN A DISH

New York, NY (November 6, 2014) – A team of scientists led by The New York Stem Cell Foundation (NYSCF) Research Institute successfully created a human stem cell disease model of Parkinson's disease in a dish. Studying a pair of identical (monozygotic) twins, one affected and one unaffected with Parkinson's disease, another unrelated Parkinson's patient, and four healthy control subjects, the scientists were able to observe key features of the disease in the laboratory, specifically differences in the patients' neurons' ability to produce dopamine, the molecule that is deficient in Parkinson's disease. In addition, the scientists also identified a potential strategy for developing novel therapies for Parkinson's disease.

Attributed to a combination of genetic and nongenetic factors, Parkinson's disease has no completely effective therapy or cure. Parkinson's disease is moderately heritable, but the mechanisms of this inheritance are not well understood. While genetic forms of the disease exist, sporadic forms are far more common.

“The unique scenario of identical twins, one with this disease and one without, allowed our scientists an unprecedented look into the mechanisms of Parkinson's disease,” said Susan L. Solomon, NYSCF Chief Executive Officer. “Advanced stem cell research techniques allow us to push the boundaries of science and see what actually goes wrong at the cellular level, step by step during the disease process.”

DNA mutations resulting in the production of a specific enzyme called glucocerebrosidase (GBA) have been linked to a five-fold greater risk of developing Parkinson's disease; however, only 30% of individuals with this mutation have been shown to develop Parkinson's disease by the age of 80. This discordance suggests that multiple factors contribute to the development of Parkinson's disease, including both genetic and non-genetic factors. To date, there has been no appropriate model to identify and test multiple triggers leading to the onset of the disease.

In this study, published today in *Cell Reports*, a set of identical twins, both with a GBA mutation, provided a unique opportunity to evaluate and dissect the genetic and non-genetic contributions to the development of Parkinson's disease in one twin, and the lack of disease in the other. The scientists made induced pluripotent stem (iPS) cells from skin samples from both twins to generate a cellular model of Parkinson's in a dish, recapitulating key features of the disease, specifically the accumulation of α -synuclein and dopamine deficiency.

Upon analyzing the cell models, the scientists found that the dopamine-producing neurons from both twins had reduced GBA enzymatic activity, elevated α -synuclein protein levels, and a reduced capacity to synthesize and release dopamine. In comparison to his unaffected brother, the neurons generated from the affected twin produced less dopamine, had higher levels of an enzyme called monoamine oxidase B (MAO-B), and poor ability to connect with each other. Treating the neurons with molecules that lowered the activity of MAO-B together with overexpressed GBA normalized α -synuclein and dopamine levels in the cell models. This suggests that a combination therapy for the affected twin may be possible by simultaneously targeting these two enzymes.

“The subject of Parkinson's disease discordant twins gave us an incredible opportunity to utilize stem cell models of disease in a dish to unlock some of the biological mechanisms of disease,” said Dr. Scott Noggle, NYSCF Vice President, Stem Cell Research and The NYSCF – Charles Evans Senior Research Fellow for Alzheimer's Disease. “Working with these various different groups and scientists added to the depth and value of the research and we hope our findings will be applicable to other Parkinson's disease patients and other neurodegenerative disorders.”

In this particular scenario, genetic and stem cell analysis identified an avenue for a potentially useful combination therapy for the twin affected by Parkinson's disease and may be applicable more broadly to other Parkinson's patients. While this case study is unique, this type of research and cellular analysis could yield further clues to all cases of genetic and sporadic Parkinson's disease and other related neurological disorders.

This study was conducted in collaboration with scientists at New York University Langone Medical Center including Dr. Melissa Nirenberg, Columbia University, Harvard University, the Icahn School of Medicine at Mount Sinai, Axion Biosystems, and Genzyme Corporation. Chris Woodard and Brian Campos of The New York Stem Cell Foundation Research Institute were the co-first authors of the study and Dr. Scott Noggle and Dr. Aiqun Li of The New York Stem Cell Foundation Research Institute and Dr. Sheng-Han Kuo of Columbia University Medical Center were the corresponding authors for the study.

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 70 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 several major discoveries in the field, including: the first diploid stem cell line from a patient with type 1 diabetes using somatic cell nuclear transfer in April 2014; 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.