NYSCF
The New York Stem Cell Foundation

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SCIENTISTS AT THE NEW YORK STEM CELL FOUNDATION AND COLUMBIA UNIVERSITY MEDICAL CENTER DEVELOP SCIENTIFIC TECHNIQUE TO HELP PREVENT INHERITED DISORDERS IN HUMANS

A new study published in Nature *shows how mitochondrial disease may be prevented*

NEW YORK, NY (December 19, 2012) – A joint team of scientists from The New York Stem Cell Foundation (NYSCF) Laboratory and Columbia University Medical Center (CUMC) has developed a technique that may prevent the inheritance of mitochondrial diseases in children. The study is published online today in *Nature*.

Dieter Egli, PhD, and Daniel Paull, PhD, of the NYSCF Laboratory with Mark Sauer, MD, and Michio Hirano, MD, of CUMC demonstrated how the nucleus of a cell can be successfully transferred between human egg cells. This landmark achievement carries significant implications for those children who have the potential to inherit mitochondrial diseases.

Mitochondria are cellular organelles responsible for the maintenance and growth of a cell. They contain their own set of genes, passed from mother to child, and are inherited independently from the cell's nucleus. Although mitochondrial DNA accounts for only 37 out of more than 20,000 genes in an individual, mutations to mitochondrial genes carry harmful effects.

Mitochondrial disorders, due to mutations in mitochondrial DNA, affect approximately 1 in 10,000 people, while nearly 1 in 200 individuals carries mutant mitochondrial DNA. Symptoms, manifesting most often in childhood, may lead to stunted growth, kidney disease, muscle weakness, neurological disorders, loss of vision and hearing, and respiratory problems, among others. Worldwide, a child is born with a mitochondrial disease approximately every 30 minutes, and there are currently no cures for these devastating diseases.

"Through this study, we have shown that it should be possible to prevent the inheritance of mitochondrial disorders," said Egli, PhD, co-author of the study and an Senior Researcher in the NYSCF Laboratory. "We hope that this technique can be advanced quickly toward the clinic where studies in humans can show how the use of this process could help to prevent mitochondrial disease."

In this study, the researchers removed the nucleus of an unfertilized egg cell and replaced it with the nucleus of another donor's egg cell. The resultant egg cell contained the genome of the donor but not her mitochondrial DNA. The researchers demonstrated that the transfer did not have detectable adverse effects on the egg cell, a prerequisite for clinical translation. They achieved this by lowering the temperature of the egg before nuclear transfer, a novel technique. Previous studies report adverse consequences in approximately 50% of the egg cells.

The researchers then artificially activated the egg cell through a technique called parthenogenesis and derived stem cell lines from the blastocyst that developed. These cell lines were grown for

more than a year and generated adult cell types such as neurons, heart cells and pancreatic beta cells that are affected by mutant mitochondrial DNA. They found the levels of the donated genome's original mitochondria to be undetectable, demonstrating that this would permanently eliminate the mitochondrial DNA and prevent a family's future generations from developing these diseases.

Current treatment options to prevent mitochondrial disease are limited. A woman with a family history of mitochondrial disease may abstain from having children. She may alternatively elect to undergo in vitro fertilization (IVF) with donor eggs; however, this means the child will be genetically unrelated to her. As another option, patients can undergo IVF treatment and, through prenatal screening, to allow clinicians to select from a mother's eggs those that have the least likelihood of carrying mitochondrial DNA defects. This is not, however, a fully effective screening process, and her children may still be affected by mitochondrial disorders.

"Women who carry mutant mitochondrial DNA may no longer have to worry that their children will become sick. This technique may allow us to provide women with a therapeutic option that will prevent these disorders," said Sauer, MD, a co-author on the paper and Vice Chairman of the Department of Obstetrics and Gynecology and Chief of Reproductive Endocrinology at Columbia University Medical Center. Sauer is also Program Director of Assisted Reproduction at the Center for Women's Reproductive Care.

"These findings epitomize the goals and aspirations of The New York Stem Cell Foundation – to accelerate and find cures, and prevent diseases," said Susan L. Solomon, CEO of The New York Stem Cell Foundation. "This research underscores the importance of interdisciplinary collaborations in which close partnerships between researchers and clinicians allow for tremendous advances that previously were not possible."

"We often know too late that a patient runs the risk of passing on defective mitochondria to her children. It is absolutely devastating to a patient and her family," said Hirano, MD, Professor of Neurology and Co-Director of the Adult Muscular Dystrophy Association clinic at Columbia University Medical Center, where he sees patients with mitochondrial disease. "This new technique offers an effective solution by ensuring only healthy mitochondria are present in the egg cells."

The scientists plan to move toward clinical application using this technique. Next steps include the production of more mitochondrial disease-free egg cells and the generation of healthy progeny in an animal model.

The research was conducted in the New York Stem Cell Foundation Laboratory in Manhattan and in collaboration with Columbia University Medical Center clinicians and researchers.

Funding for this research was provided by private sources and New York State. The oocyte donations required for the research adhered to ethical guidelines of the American Society for Reproductive Medicine and the International Society for Stem Cell Research as well as protocols reviewed and approved by the institutional review board and stem cell committees of Columbia University Medical Center. Additionally, the Nuffield Council on Bioethics, a British organization, has endorsed this line of research to prevent mitochondrial disease.

The New York Stem Cell Foundation (NYSCF) conducts advanced stem cell research in its own laboratory and supports research by stem cell scientists at other institutions around the world. More information is available at www.nyscf.org.

Columbia University Medical Center (CUMC) provides international leadership in basic, pre-clinical and clinical research, in medical and health sciences education, and in patient care. More information is available at www.cumc.columbia.edu.