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NYSCF AND COLUMBIA RESEARCHERS DEMONSTRATE USE OF STEM CELLS TO ANALYZE CAUSES AND TREATMENT OF DIABETES

Using patient-specific stem cells to correct deficient insulin-producing cells

NEW YORK, NY (June 17, 2013) – A team from the New York Stem Cell Foundation (NYSCF) Research Institute and the Naomi Berrie Diabetes Center of Columbia University has generated patient-specific beta cells, or insulin-producing cells, that accurately reflect the features of maturity-onset diabetes of the young (MODY).

The researchers used skin cells of MODY patients to produce induced pluripotent stem (iPS) cells, from which they then made beta cells. Transplanted into a mouse, the stem cell-derived beta cells secreted insulin in a manner similar to that of the beta cells of MODY patients. Repair of the gene mutation restored insulin secretion to levels seen in cells obtained from healthy subjects. The findings were reported today in the *Journal of Clinical Investigation*.

Previous studies have demonstrated the ability of human embryonic stem cells and iPS cells to become beta cells that secrete insulin in response to glucose or other molecules. But the question remained as to whether stem cell-derived beta cells could accurately model genetic forms of diabetes and be used to develop and test potential therapies.

"We focused on MODY, a form of diabetes that affects approximately one in 10,000 people. While patients and other models have yielded important clinical insights into this disease, we were particularly interested in its molecular aspects—how specific genes can affect responses to glucose by the beta cell," said co-senior author Dieter Egli, PhD, Senior Research Fellow at NYSCF, who was named a NYSCF–Robertson Stem Cell Investigator in 2012.

MODY is a genetically inherited form of diabetes. The most common form of MODY, type 2, results in a loss-of-function mutation in one copy of the gene that codes for the sugar-processing enzyme glucokinase (GCK). With type 2 MODY, higher glucose levels are required for GCK to metabolize glucose, leading to chronic, mildly elevated blood sugar levels and increased risk of vascular complications.

MODY patients are frequently misdiagnosed with type 1 or 2 diabetes. Proper diagnosis can not only change the patient's course of treatment but affect family members, who were previously unaware that they, too, might have this genetic disorder.

NYSCF scientists took skin cells from two Berrie Center type 2 MODY patients and "reprogrammed"—or reverted—them to an embryonic-like state to become iPS cells. To examine the effect of the GCK genetic mutation, they also created two genetically manipulated iPS cell lines for comparison: one fully functional (two correct copies of the GCK gene) and one with complete loss of function (two faulty copies of the GCK gene). They then generated beta cell precursors from the fully functional and loss-of-function iPS cell lines and transplanted the cells for further maturation into immune-compromised mice.

"Our ability to create insulin-producing cells from skin cells, and then to manipulate the GCK gene in these cells using recently developed molecular methods, made it possible to definitively test several critical aspects of the utility of stem cells for the study of human disease," said Haiqing Hua, PhD, lead author on the paper, a postdoctoral fellow in the Division of Molecular Genetics, Department of Pediatrics and Naomi Berrie Diabetes Center at Columbia University and the New York Stem Cell Foundation Research Institute.

When given a glucose tolerance test three months later, mice with MODY beta cells had decreased sensitivity to glucose but a normal response to other molecules that stimulate insulin secretion. This is the hallmark of MODY. Mice with two faulty copies of the GCK gene secreted no additional insulin in response to glucose. When the researchers repaired the GCK mutation using molecular techniques, cells with two restored copies of GCK responded normally to the glucose stress test. Unlike other reported techniques, the researchers' approach efficiently repaired the GCK mutation without introducing any potentially harmful additional DNA.

"Generation of patient-derived beta cells with gene correction could ultimately prove to be a useful cell-replacement therapy by restoring patients' ability to regulate their own glucose. This result is truly exciting," said Susan L. Solomon, Chief Executive Officer of The New York Stem Cell Foundation.

The researchers also used an electron microscope to assess beta cells for insulin content by counting granules—packages that store insulin for release. Even though all beta cell types had a similar number of granules, complete loss of function of the GCK gene was associated with decreased beta-cell production.

"These studies provide a critical proof-of-principle that genetic characteristics of patient-specific insulin-producing cells can be recapitulated through use of stem cell techniques and advanced molecular biological manipulations. This opens up strategies for the development of new approaches to the understanding, treatment, and, ultimately, prevention of more common types of diabetes," said co-senior author Rudolph Leibel, MD, Christopher Murphy Memorial Professor of Diabetes Research, Columbia University Medical Center, and Director, Division of Molecular Genetics, and Co-Director of the Naomi Berrie Diabetes Center.

The other authors are: Linshan Shang and Hector Martinez of the New York Stem Cell Foundation Research Institute; and Matthew Freeby, Mary Pat Gallagher, Thomas Ludwig, Liyong Deng, Ellen Greenberg, Charles LeDuc, Wendy K. Chung, and Robin Goland of the Division of Molecular Genetics, Department of Pediatrics, and Naomi Berrie Diabetes Center at Columbia University.

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The authors report no financial or other conflict of interest.

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 40 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 four major discoveries in the field, including: the discovery of a clinical cure to prevent transmission of maternal 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 Naomi Berrie Diabetes Center

Upon its official opening in October 1998, the **Naomi Berrie Diabetes Center** at Columbia University Medical Center established a new standard of care for the 1.6 million people with diabetes in the New York area—combining world-class diabetes research and education programs with unprecedented family-oriented patient care. Founded with support from the Russell Berrie Foundation and other friends, and named in honor of the mother of the late Russell Berrie, founder of RUSS™ Toys, the center is today recognized as the most comprehensive diabetes research and treatment center in the tri-state region and has been designated a national "Diabetes Center of Excellence" —one of only three in the state of New York. Approximately one hundred and fifty clinicians and scientists, affiliated with the

Center, conduct basic and clinical research related to the pathogenesis and treatment of all forms of diabetes and its complications. For more information, visit nbdiabetes.org.

Drs. Chung and Leibel are also members of the **Columbia Stem Cell Initiative** (www.ColumbiaStemCell.org), which brings together the many scientists and clinicians at Columbia focused on tapping the potential of stem cells for human health.

About Columbia University Medical Center

Columbia University Medical Center provides international leadership in basic, preclinical, and clinical research; medical and health sciences education; and patient care. The medical center trains future leaders and includes the dedicated work of many physicians, scientists, public health professionals, dentists, and nurses at the College of Physicians and Surgeons, the Mailman School of Public Health, the College of Dental Medicine, the School of Nursing, the biomedical departments of the Graduate School of Arts and Sciences, and allied research centers and institutions. Columbia University Medical Center is home to the largest medical research enterprise in New York City and State and one of the largest faculty medical practices in the Northeast. For more information, visit cumc.columbia.edu or columbiadoctors.org.

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