Developing stem cell model for Gaucher disease, neurodegenerative conditions

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A new method of using adult stem cells as a model for the hereditary condition Gaucher disease could help accelerate the discovery of new, more effective therapies for this and other conditions such as Parkinson's, according to new research from the University of Maryland School of Medicine.

Scientists at the University of Maryland School of Medicine reprogrammed stem cells to develop into cells that are genetically similar to and react to drugs in a similar way as cells from patients with Gaucher disease. The stem cells will allow the scientists to test potential new therapies in a dish, accelerating the process toward drug discovery, according to the paper published online in the journal the Proceedings of the National Academy of Sciences (*PNAS*) on Oct. 15 (Panicker et.al.).

"We have created a model for all three types of Gaucher disease, and used stem cell-based tests to evaluate the effectiveness of therapies," says senior author Ricardo Feldman, Ph.D., associate professor of microbiology and immunology at the University of Maryland School of Medicine, and a research scientist at the University of Maryland Center for Stem Cell Biology and Regenerative Medicine. "We are confident that this will allow us to test more drugs faster, more accurately and more safely, bringing us closer to new treatments for patients suffering from Gaucher disease. Our findings have potential to help patients with other neurodegenerative diseases as well. For example, about 10 percent of Parkinson's disease patients carry mutations in the recessive gene for Gaucher disease, making our research possibly significant for

Parkinson's disease as well."

Gaucher disease is the most frequent lipid-storage disease. It affects 1 in 50,000 people in the general population. It is most common in Ashkenazi Jews, affecting 1 in 1,000 among that specific population. The disease occurs in three subtypes—Type 1 is the mildest and most common form of the disease, causing symptoms such as enlarged livers and spleens, anemia and bone disease. Type 2 causes very serious brain abnormalities and is usually fatal before the age of two, while Type 3 affects children and adolescents.

The condition is a recessive genetic disorder, meaning that both parents must be carriers for a child to suffer from Gaucher. However, said Dr. Feldman, studies have found that people with only one copy of a mutated Gaucher gene—those known as carriers—are at an increased risk of developing Parkinson's disease.

"This science is a reflection of the mission of the University of Maryland School of Medicine—to take new treatments from bench to bedside, from the laboratory to patients, as quickly as possible," says E. Albert Reece, M.D., Ph.D., M.B.A., vice president for medical affairs at the University of Maryland and John Z. and Akiko K. Bowers Distinguished Professor and dean of the University of Maryland School of Medicine. "We are excited to see where this research goes next, bringing new hope to Gaucher patients and their families."

Dr. Feldman and his colleagues used the new reprogramming technology developed by Shinja Yamanaka in Japan, who was recognized with this year's Nobel Prize for Medicine or Physiology. Scientists engineered cells taken from the skin of Gaucher patients, creating human induced pluripotent stem cells, known as hiPSC—stem cells that are theoretically capable of forming any type of cell in the body. Scientists differentiated the cells to form white blood cells known as macrophages and neuronal

cells.

A key function of macrophages in the body is to ingest and eliminate damaged or aged red blood cells. In Gaucher disease, the macrophages are unable to do so—they can't digest a lipid present in the red blood cell membrane. The macrophages become engorged with lipid and cannot completely clear the ingested red blood cells. This results in blockage of membrane transport pathways in the macrophages lodged in the bone marrow, spleen and liver. The macrophages that the scientists created from the reprogrammed stem cells exhibited this characteristic hallmark of the macrophages taken from Gaucher patients.

To further test the stem cells, the scientists administered a recombinant enzyme that is effective in treating Gaucher patients with Type 1 disease. When the cells were treated with the enzyme, the function of the macrophages was restored—they completely cleared the red blood cells.

"The creation of these stem cell lines is a lovely piece of stem cell research," said Curt Civin, M.D., professor of pediatrics and physiology, associate dean for research and founding director of the Center for Stem Cell Biology & Regenerative Medicine at the University of Maryland School of Medicine. "Dr. Feldman is already using these Gaucher patient-derived macrophages to better understand the disease fundamentals and to find novel medicines for Gaucher disease treatment. A major goal of our Center for Stem Cell Biology & Regenerative Medicine is to translate our fundamental discoveries into innovative and practical clinical applications that will enhance the understanding, diagnosis, treatment, and prevention of many human diseases. Clinical applications include not only transplantation of stem cells, but also the use of stem cells for drug discovery as Dr. Feldman's studies so beautifully illustrate."

"We are looking forward to testing new drugs on these cells, getting new

therapies to patients," says Dr. Feldman.

Provided by University of Maryland