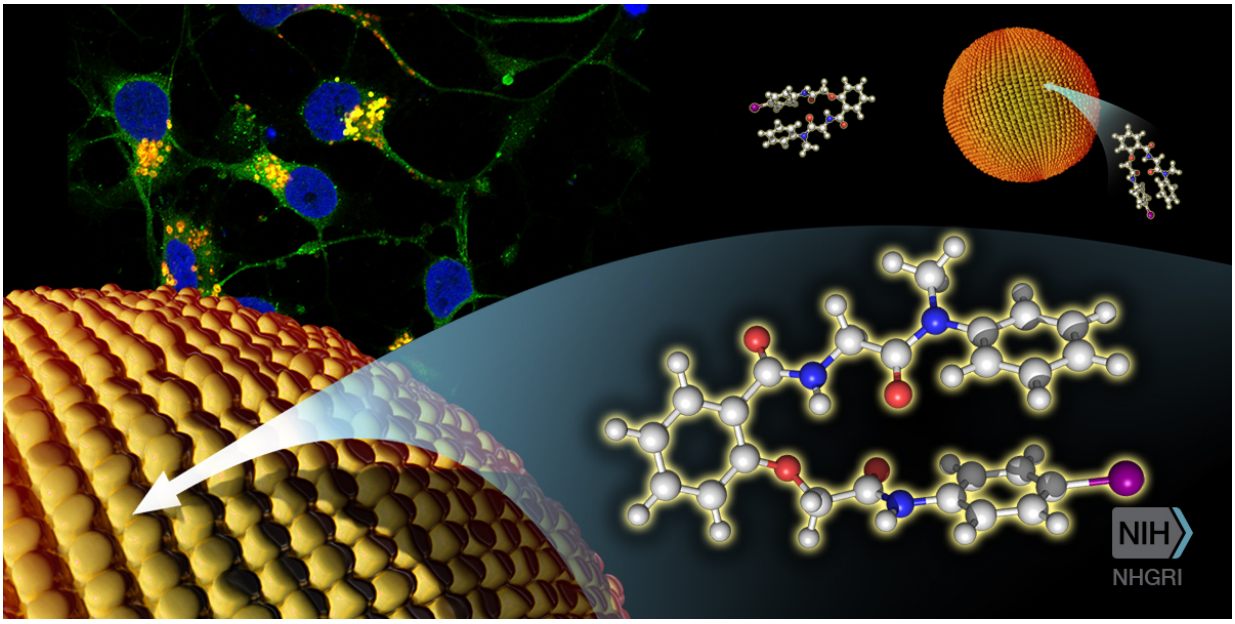
Researchers make advance in possible treatments for Gaucher, Parkinson's diseases

July 12 2016



NIH researchers identified the small molecule NCGC607 that chaperones the mutated protein (glucocerebrosidase) to the lysosomes of the nerve cells (neurons). The molecule helps the lysosomes break down the cell's waste products (lipids). Credit: Darryl Leja, NHGRI

With assistance from a high tech robot known at Tox21, National Institutes of Health researchers have identified and tested a molecule that shows promise as a possible treatment for the rare Gaucher disease and the more common Parkinson's disease. Ellen Sidransky, M.D., a

senior investigator with NIH's National Human Genome Research Institute (NHGRI), and her collaborators at the National Institute of Neurological Disorders and Stroke (NINDS) and the National Center for Advancing Translational Sciences (NCATS), published their findings June 12, 2016 in the *Journal of Neuroscience*.

"Until now, drugs used to treat Gaucher disease have not been able to enter the brain and reach those neurons that are affected in the most severe forms of Gaucher disease or in Parkinson's disease," said Dr. Sidransky. "It's really exciting to have found a molecule that theoretically could be widely available to treat people with these diseases. However, there's a long distance between identifying this molecule and having an approved drug." Dr. Sidransky has conducted research on Gaucher disease for the last 28 years and made the connection between Gaucher disease and Parkinson's disease in 2001.

Gaucher disease occurs when GBA1, the gene that codes for the protein glucocerebrosidase, is mutated. This protein normally helps cells dispose of certain fats (lipids), a type of waste produced by all cells. When a person inherits two mutated copies of GBA1, lipids accumulate and can cause symptoms such as enlargement of the spleen, frequent bleeding and bruising, weakened bones and, in the most severe cases, neurological disease. People with even one mutated copy of GBA1 are at higher risk of developing Parkinson's disease, a common disorder characterized by tremors, muscular rigidity and slowed movements.

To better understand the connection between Gaucher and Parkinson's diseases, NHGRI researchers used a labor-intensive technology to develop pluripotent stem cells (unspecialized cells that can develop into various specialized body cells). Elma Aflaki, Ph.D., a research fellow in Sidransky's lab, created stem cells from the skin cells of Gaucher patients with and without Parkinson's disease in the lab. She then converted the stem cells into neurons that had features that were

identical to those in people with Gaucher disease. Neurons are nerve cells that transmit information via chemical messengers and electrical signals.

The researchers showed that the neurons from Gaucher patients, who also had Parkinson's disease, showed elevated levels of alpha-synuclein. This is the protein that accumulates in the brains of people with Parkinson's disease impacting neurons responsible for controlling movement.

The researchers then looked for a molecule that would help patients with mutant GBA1 break down cellular waste. In a process known as high-throughput drug screening, researchers at NCATS Chemical Genomics Center used the Tox21 robot to evaluate hundreds of thousands of different molecules. NCATS researchers Juan Marugan, Ph.D., Samarjit Patnaik, Ph.D., Noel Southall, Ph.D., and Wei Zheng, Ph.D., identified a promising molecule, NCGC607, in conjunction with researchers at the University of Kansas, Lawrence, which helps to "chaperone" the mutated protein so that it can still function. In the patients' stem cell-derived neurons, NCGC607 reversed the lipid accumulation and lowered the amount of alpha-synuclein, suggesting a possible treatment strategy for Parkinson's disease.

"This research constitutes a major advance," said Daniel Kastner, M.D., Ph.D., NHGRI scientific director and director of the institute's Division of Intramural Research. "It demonstrates how insights from a rare disorder such as Gaucher disease can have direct relevance to the treatment of common disorders like Parkinson's disease."

Researchers will next test the new molecule to see if it might be developed into an appropriate prototype drug for patients with Gaucher disease and Parkinson's disease.

Gaucher disease affects an estimated 1 in 50,000 to 1 in 100,000 people in the general population. People of Eastern and Central European (Ashkenazi) Jewish heritage are more likely to get Gaucher disease. Parkinson's disease affects 1.5-2 percent of people over age 60, and the incidence increases with age. In the United States, about 60,000 new cases are identified each year. Parkinson's disease affects more than 1 million people in North America and 7-10 million people worldwide.

Provided by NIH/National Human Genome Research Institute