THE Sun

HOPE ON DEMENTIA

BY TONY WHITFIELD

Article Release: December 26, 2016

A SINGLE protein could "cure" Alzheimer's and Parkinson's, a new study found. Controlling levels of the protein could lead to new treatments for degenerative brain diseases such as Huntington's.

Such disorders are triggered when proteins in the brain misbehave and accumulate in cells, damaging and killing them. But a new study by the Gladstone Institutes in San Francisco, California, used a different protein, Nrf2, to restore levels of the disease-causing proteins to a normal, healthy range and stop cell death. Professor Dr. Steven Finkbeiner, a senior investigator and author, said: "I am very enthusiastic about this strategy for treating neurodegenerative diseases.

Such disorders are triggered when proteins in the brain misbehave and kill cells, "We've tested Nrf2 in models of Huntington's disease, Parkinson's disease, and ALS, and it is the most protective thing we've ever found. "Based on the magnitude and the breadth of the effect, we really want to understand Nrf2 and its role in protein regulation better."

The study, published in the Proceedings of the National Academy of Sciences, tested Nrf2 in two models of Parkinson's disease: cells with mutations in the proteins LRRK2 and α-synuclein. Regulating levels of the protein could lead to the development of new treatments. By activating Nrf2, the researchers turned on several "house-cleaning" mechanisms in the cell to remove excess LRRK2 and α-synuclein.

First author and staff research scientist Dr Gaia Skibinski said: "Nrf2 coordinates a whole program of gene expression, but we didn't know how important it was for regulating protein levels until now. "Overexpressing Nrf2 in cellular models of Parkinson's disease resulted in a huge effect. "In fact, it protects cells against the disease better than anything else we've found."

The study used rat neurons and human neurons created from induced pluripotent stem cells which were then programmed to express Nrf2 and either mutant LRRK2 or α-synuclein. Using a one-of-a-kind robotic microscope developed by Prof Finkbeiner's laboratory, the researchers tagged and tracked individual neurons over time to monitor their protein levels and overall health. Thousands of images of the cells were taken over the course of a week, measuring the development and demise of each one. It was discovered Nrf2 worked in different ways to help remove either mutant LRRK2 or α-synuclein from the cells. For mutant LRRK2, Nrf2 drove the protein to gather into incidental clumps that can remain in the cell without damaging it. For α-synuclein, Nrf2 accelerated the breakdown and clearance of the protein, reducing its levels in the cell.

While Nrf2 itself may be difficult to target with a drug because it is involved in so many cellular processes, some of its downstream effects could provide the key. Scientists hope to identify other players in the protein regulation pathway that interact with Nrf2 to improve cell health and that may be easier to drug.