Lowering levels of toxic protein reverses abnormalities in cells from patients with fatal brain disease

UCL scientists, in collaboration with colleagues at the University of Massachusetts Medical School, have shown for the first time that switching off the mutant protein that causes the fatal brain disorder Huntington’s disease can reverse abnormalities in living cells taken from patients with the disease. Drugs that aim to ‘silence’ the mutant protein are likely to enter clinical trials in the next few years, and this research, published in Brain, is the first time that a drug that partially reduces the levels of the mutant protein has some beneficial effect in cells from Huntington’s disease patients, suggesting that the protein does not need to be completely depleted to delay or reverse harmful effects of Huntington’s disease.

Huntington’s disease is an incurable genetic neurological disease that usually develops in adulthood and causes abnormal involuntary movements, psychiatric symptoms and dementia. It is caused by a genetic mutation that causes production of a harmful protein, called mutant huntingtin, which is produced not just in the brain, but in every cell of a patient’s body.

The research team, led by Professor Sarah Tabrizi at the UCL Institute of Neurology, was made up of scientists from around the world. They compared specific immune cells, called monocytes, from blood samples donated by Huntington’s disease patients and healthy volunteers. The cells from Huntington’s disease patients respond excessively when exposed to a chemical from bacteria that causes an immune response. This results in the cells producing increased levels of inflammatory molecules. Inflammation is usually beneficial in helping clear infection, but in excess it can be damaging to the brain and other tissues.

To reduce levels of the mutant protein, the team went on to take advantage of the cells’ natural ability to engulf and digest foreign agents, such as bacteria and fungi. The cells were fed sugar-coated glucan particles containing a drug molecule (siRNA) that partially silenced the mutant huntingtin gene, leading to a reduction in levels of the harmful protein. This dampened the excessive response of the cells to immune stimulation. They also showed that mutant huntingtin interacts with an enzyme, IKK, inside the cells that controls the switching on of certain genes, including those encoding the inflammatory molecules produced by the cells.

“This is the first time that disease-associated alterations in cell function have been reversed in cells taken directly from Huntington’s disease patients,” said Professor Tabrizi. “That lowering of the toxic form of the huntingtin protein reverses the effects of the disease in easily obtained blood samples from patients, offers encouragement that such treatments may have similar effects in the brains of patients to slow the process of degeneration in Huntington’s disease.”

These findings also shed light on how the protein affects the immune system to exert damaging effects beyond those caused directly in the brain.
“These findings improve our understanding of the role of the immune system in Huntington’s disease and other neurodegenerative disorders,” continued Professor Tabrizi. “They also raise the prospect of targeting the mutant huntingtin protein in blood cells as a possible therapeutic approach in Huntington’s disease.”

Background
Huntington’s disease is a fatal genetic neurological disease. It usually develops in adulthood and causes abnormal involuntary movements, psychiatric symptoms and dementia. It is incurable, and no effective treatments exist to slow it down. Patients usually die within 20 years of the start of symptoms. HD is caused by a single known genetic mutation, and each child of a carrier of the mutation has a 50% chance of inheriting the disease.

Green glucan encapsulated siRNA particles (GeRPs) are phagocytosed by human monocytes (as shown) and macrophages to effectively knock-down total HTT in these cells. This reverses the hyper-reactivity of Huntington’s disease monocytes and macrophages to immune stimuli.