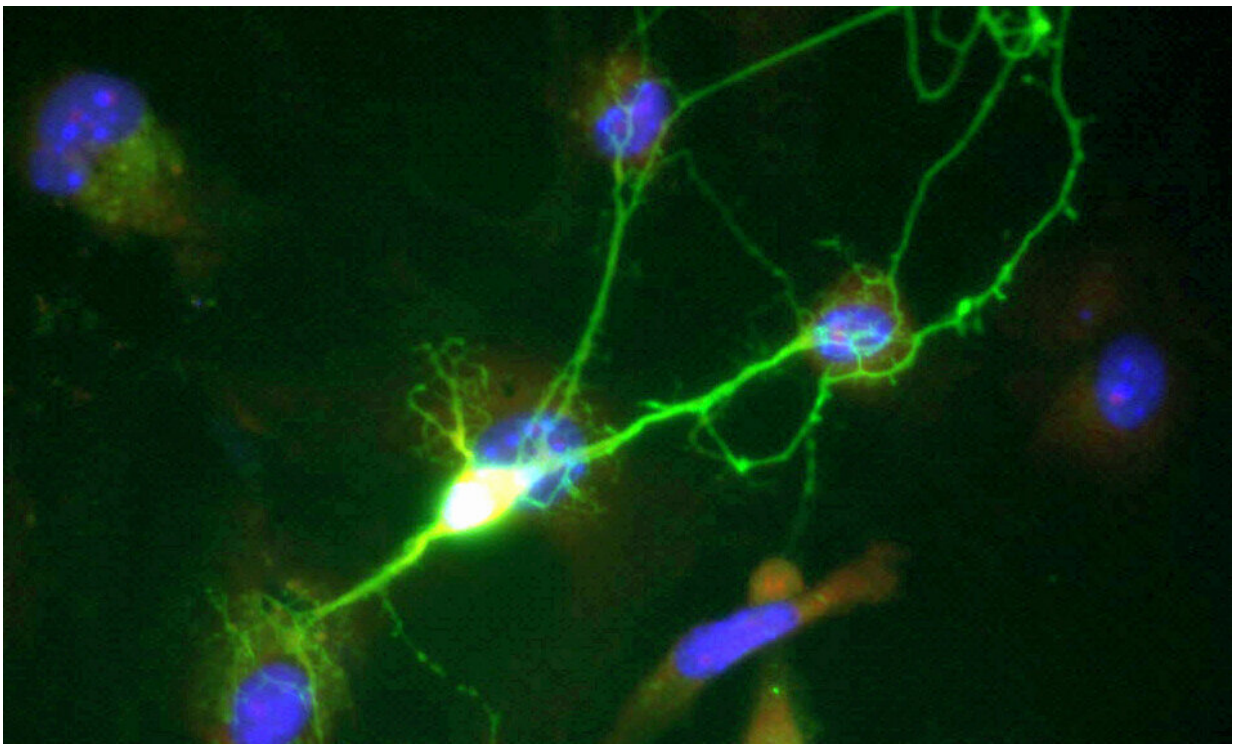
Scientists discover how to prevent death of nerve cells in most common genetic forms of MND and dementia

March 1 2023



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Scientists have found a novel way to block the transportation of mutant RNA and subsequent production of toxic repeat proteins that lead to the death of nerve cells in the most common subtypes of motor neuron

disease (MND) and frontotemporal dementia (FTD).

The new study, conducted by researchers at the University of Sheffield's Institute of Translational Neuroscience (SITraN), also showed that using a peptide to stop the transport of mutant repeated RNA molecules and production of toxic repeat proteins actually increases the survival of C9ORF72 nerve cells—protecting them against neurodegeneration.

The Sheffield team previously discovered the abnormal transportation of the rogue RNAs copied from the C9ORF72 gene—known to be the most frequent cause of MND and FTD—is caused by excessive stickiness of a cell transporter named SRSF1.

Instead of using conventional drugs, which are inefficient in disrupting the stickiness of the SRSF1 protein, or invasive therapies to edit or modulate the activity of defective genes, the new study found that a small peptide incorporating a cell-penetrating module can stick to SRSF1 and effectively block the transportation of the rogue repeat RNA.

The peptide is composed of a short chain of amino acids or bricks found within our cells and tissues in the body.

Interestingly, the findings, published in the journal *Science Translational Medicine* also suggest the peptide could be given to MND and FTD patients orally in a non-invasive manner—for example through a nasal spray which could be developed to enter the brain.

This groundbreaking concept of using peptides to block the effects of the damaging repeat expanded RNA and toxic repeat proteins could transform how some neurodegenerative conditions which currently have no cure are treated.

Professor Guillaume Hautbergue, Professor of Translational RNA

Biology at the University of Sheffield, who led the study said, "When we tested our innovative approach by adding the peptide to the food eaten by fruit flies not only did the peptides block the damaging mutations which cause MND and FTD from being transported to the cell's nucleus, we actually saw an improvement in their neurofunction.

"This means the peptide is effectively blocking the progression of the neurodegenerative condition and also helping to restore the function to the affected nerve cells.

"This concept of using peptides to block destructive mutations unlocks such an exciting and innovative treatment pathway which until now has not been explored by scientists.

"MND and FTD are devastating diseases which currently have no cure. This is a promising alternative to conventional small molecule drugs which are often limited by poor penetration of the blood-brain barrier."

FTD occurs when nerve cells in the frontal and temporal lobes of the brain are lost, causing the lobes to shrink. FTD most commonly affects people aged 45–65 and can affect behavior, personality, language and movement. There is no cure for FTD, and no treatments available to slow or stop the progression of the disease.

MND is a debilitating condition that destroys the cells that control movement, leaving sufferers unable to move, walk, talk and eventually breathe. Treatments are very limited and there is no cure. Most patients with the disease are only expected to live two to five years after diagnosis. This study was made possible thanks to donated tissue samples from the skin of MND patients which were reprogrammed into nerve cells.

Dr. Brian Dickie, Director of Research at the MND Association, said,

"These findings from a world leading research team in Sheffield demonstrate the importance of funding fundamental 'discovery' science. This work has provided important evidence in support of a completely new strategy to treat the most common inherited cause of both MND and FTD, with the ultimate goal of developing effective therapies for these devastating diseases."

More information: Lydia Castelli et al, A cell-penetrant peptide blocking C9ORF72-repeat RNA nuclear export reduces the neurotoxic effects of dipeptide repeat proteins, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.abo3823. www.science.org/doi/10.1126/scitranslmed.abo3823

Provided by University of Sheffield