New method delivers Alzheimer’s drug to the brain

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Oxford University scientists have developed a new method for delivering complex drugs directly to the brain, a necessary step for treating diseases like Alzheimer’s, Parkinson’s, Motor Neuron Disease and Muscular Dystrophy.

These diseases have largely resisted attempts to over the last 50 years develop new treatments, partly because of the difficulty of getting effective new drugs to the brain to slow or halt disease progression.

The team has successfully switched off a gene implicated in Alzheimer’s disease in the brains of mice by exploiting exosomes – tiny particles naturally released by cells.

The exosomes, injected into the blood, are able to ferry a drug across the normally impermeable blood-brain barrier to the brain where it is needed.

Although this is a significant and promising result, there are a number of steps to be taken before this new form of drug delivery can be tested in humans in the clinic.

The study, partly funded by the Muscular Dystrophy Campaign, is published in Nature Biotechnology.‘

These are dramatic and exciting results.

It’s the first time new “biological” medicines have been delivered effectively across the blood-brain-barrier to the brain,’ says Dr Matthew Wood of the Department of Physiology, Anatomy and Genetics at the University of Oxford, who led the work.

Exosomes are small capsules that are produced by most cells in the body in varying amounts.

These natural nanoparticles are thought to be one of the ways cells communicate with each other and the body’s immune system.

When exosomes break off from the outer walls of cells, they can take various cellular signals and genetic material with them, transporting this material between different cells.

This led the Oxford University researchers to wonder whether exosomes could be adapted for delivering drugs to different cells and tissues of the body.

‘This is the first time this natural system has been exploited for drug delivery,’ says Dr Wood.

Novel drugs based on antibodies, peptides or more recently RNA molecules have been developed on many occasions to target specific parts of disease pathways.

While these have shown good results in the lab, too often it has proved difficult to get the drugs to the right part of the body to see any effect in humans.

Currently, delivering any such type of therapy to the brain would have to involve neurosurgery. Nothing delivered intravenously would be able to cross from the blood into the brain.‘

The major barrier for these drugs is delivery,’ explains Dr Wood.

‘This problem becomes even greater when you want to reach the brain.

The blood-brain barrier – which stops most things in the blood stream from crossing to our brains – is much too great an obstacle.’

The Oxford University team set out to adapt naturally occurring exosomes to deliver a gene therapy.

They used an RNA sequence – RNA is a molecule related to DNA that also caries genetic information – that switches off a gene that’s implicated in Alzheimer’s disease.

To be able to make the approach work, they would need to be able to load the exosomes with the RNA, the drug. But they would also need to be able to target the right tissues in the body.

First of all, they produced and purified exosomes from mouse cells.

They then developed and patented new methods to both insert RNA molecules into the exosomes and add protein elements into the exosome coat that would target nerve cells.

The exosomes, injected intravenously into mice, crossed the blood-brain barrier and ended up in the brain.

Once there, the RNA was able to switch off a gene implicated in the build up of malformed protein in Alzheimer’s disease.

This resulted in a 60% decrease in the brain of the problem enzyme encoded by the gene.

‘We’ve shown that a natural system could be exploited to deliver drugs across the blood-brain barrier,’ says Dr Wood.

‘We believe we can use this same technology for Alzheimer’s, motor neuron disease, Parkinson’s and Huntington’s. All we need is a different RNA each time.‘

The next steps are to test the exosomes in a mouse model of Alzheimer’s disease to see if it makes a difference to disease progression,’ Dr Wood explains.

He also notes that other steps would be needed before exosomes could be tested in humans, including safety tests and scaling up the procedures.

‘Many of these diseases have not been possible to treat in the last 50 years using standard drugs.

New drugs have been developed based on complex biological molecules – antibodies, peptides, and RNA – but all require new ways of delivering the drugs,’ he says.

‘These natural nanoparticles would be administered intravenously, or perhaps even orally, and would still reach the brain.’

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**Notes for editors**

* The paper ‘Exosome-mediated targeted systemic delivery of siRNA to the brain’ by Lydia Alvarez-Erviti and colleagues is to be published in the journal Nature Biotechnology .
* The study was funded by the Muscular Dystrophy Campaign and the Agency for Science, Technology and Research in Singapore.
* **Oxford University’s Medical Sciences Division** is one of the largest biomedical research centres in Europe. It represents almost one-third of Oxford University’s income and expenditure, and two-thirds of its external research income. Oxford’s world-renowned global health programme is a leader in the fight against infectious diseases (such as malaria, HIV/AIDS, tuberculosis and avian flu) and other prevalent diseases (such as cancer, stroke, heart disease and diabetes). Key to its success is a long-standing network of dedicated Wellcome Trust-funded research units in Asia (Thailand, Laos and Vietnam) and Kenya, and work at the MRC Unit in The Gambia. Long-term studies of patients around the world are supported by basic science at Oxford and have led to many exciting developments, including potential vaccines for tuberculosis, malaria and HIV, which are in clinical trials.
* **The Muscular Dystrophy Campaign** is the leading UK charity focusing on muscle disease. It has pioneered the search for treatments and cures for over 50 years, and is dedicated to improving the lives of all children and adults affected by muscle disease.  
    
  It funds world-class research to find effective treatments and cures; provides free practical and emotional support; campaigns to raise awareness and bring about change and awards grants towards the cost of specialist equipment, such as powered wheelchairs.  
    
  More than 70,000 babies, children and adults in the UK have muscular dystrophy or a related condition. A further 350,000 people are affected indirectly as family, friends or carers.  
    
  Using DNA and RNA as a drug offers great potential for the treatment of genetic conditions as we have seen in the recent clinical trials for Duchenne muscular dystrophy. The biggest challenge of this approach is to deliver the genetic material efficiently and safely to the cells in which it is needed and avoid potentially damaging accumulation in organs such as the liver and kidney. The Muscular Dystrophy Campaign has been funding research into this area for many years and this paper reports the discovery of a powerful method for the targeted delivery of nucleic acids and potentially other drugs. Of particular interest is the efficient delivery to the nervous system that this new method provides, which could have tremendous potential for treating conditions such as spinal muscular atrophy.