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New stem cell gene therapy gives hope to prevent inherited neurological disease

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Scientists from The University of Manchester have used stem cell gene therapy to treat a fatal genetic brain disease in mice for the first time.

The method was used to treat Sanfilippo – a fatal inherited condition which causes progressive dementia in children – but could also benefit several neurological, genetic diseases.

Researchers behind the study, published in the journal *Molecular Therapy* this month, are now hoping to bring a treatment to trial in patients within two years.

Sanfilippo, a currently untreatable mucopolysaccharide (MPS) disease, affects one in 89,000 children in the United Kingdom, with sufferers usually dying in their mid-twenties. It is caused by the lack of SGSH enzyme in the body which helps to breakdown and recycle long chain sugars, such as heparan sulphate (HS). Children with the condition build up and store excess HS throughout their body from birth which affects their brain and results in progressive dementia and hyperactivity, followed by losing the ability to walk and swallow.

Dr Brian Bigger, from the University of Manchester's Institute of Human Development who led the research, said bone marrow transplants had been used to correct similar HS storage diseases, such as Hurler syndrome, by transplanting normal cells with the missing enzyme but the technique did not work with Sanfilippo disease. This is because monocytes, a type of white blood cell, from the bone marrow, did not

produce enough enzyme to correct the levels in the brain.

Dr Bigger said: "To increase SGSH enzyme from bone marrow transplants, and to target it to the cells that traffic into the brain, we have developed a stem cell gene therapy which overproduces the SGSH enzyme specifically in bone marrow white blood cells.

"We have shown that mice treated by this method produce five times the normal SGSH enzyme levels in the bone marrow and 11 per cent of normal levels in the brain.

"The enzyme is taken up by affected brain cells and is enough to correct brain HS storage and neuro inflammation to near normal levels and completely corrects the hyperactive behaviour in mice with Sanfilippo.

"This is extremely exciting and could have huge implications for treatments. We now hope to work to a clinical trial in Manchester in 2015."

The University of Manchester team is now manufacturing a vector - a tool commonly used by molecular biologists to deliver genetic material into cells – for use in humans and hope to use this in a clinical trial with patients at Central Manchester University Hospital NHS Foundation Trust by 2015.

The stem cell gene therapy approach was recently shown by Italian scientists to improve conditions in patients with a similar genetic disease affecting the brain called metachromatic leukodystrophy, with results published in the journal Science earlier this month.

Manchester scientists refined the vector used by the Italian scientists. "This approach has the potential to treat several neurological genetic diseases," Dr Bigger added.

The research was funded by the UK MPS Society and the Sanfilippo Children's Research Foundation based in Canada.

Christine Lavery MBE, Chief Executive of the UK MPS Society, said: "Since 1970 over 130 children and young adults have lost their lives to Sanfilippo disease (MPS III) in the UK alone.

"Whilst new therapies for other MPS diseases are changing children's lives, parents of children with Sanfilippo disease can do no more than give the best possible care and live in hope that a treatment is around the corner. The positive results of Dr Brian Bigger's gene therapy programme in mice provides optimism for future generations of Sanfilippo children."

More information: doi:10.1038/mt.2013.141

Provided by University of Manchester