Gene therapy breakthrough offers hope to children with rare and fatal brain disease

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Scientists and doctors at University College London Great Ormond Street Institute of Child Health (UCL GOS ICH) and Great Ormond Street Hospital (GOSH) have given hope of a gene therapy cure to children with a rare degenerative brain disorder called Dopamine Transporter Deficiency Syndrome (DTDS).

The team have recreated and cured the disease using state-of-the-art laboratory and mouse models of the disease and will soon apply for a clinical trial of the therapy. Their breakthrough comes just a decade after the faulty gene causing the disease was first discovered by the lead scientist of this work.

The results, published in *Science Translational Medicine*, are so promising that the UK regulatory agency MHRA has advised the researchers that they can now proceed to prepare for a clinical trial. DTDS is a rare, progressive and life-limiting neurological condition caused by a faulty gene that affects brain cells. Infants with DTDS are rarely able to learn to walk or speak and as they grow they develop 'parkinsonism', so called because of similarities to Parkinson's Disease.

This includes slow movements, involuntary twisting postures of their arms and legs and whole-body stiffness.

There are no effective treatments or a cure and most children with DTDS sadly die before reaching adulthood, often from respiratory infections or other complications. Although the condition is rare, with around 50 children worldwide currently known to doctors, it has previously been mistaken for cerebral palsy and may continue to be undiagnosed.

Professor Manju Kurian discovered the faulty gene causing DTDS in 2009 and was subsequently granted seed funding worth just over £86,500 from Great Ormond Street Hospital Children's Charity (GOSH Charity) to begin developing the treatment. Professor Kurian's team and her collaborators at UCL have also spent the last decade working to better understand the mechanisms that underpin this disease, and this has enabled them to develop a new, precision gene therapy with the potential to treat this devastating disorder.

How the precision gene therapy works

Scientists took skin cells from children with DTDS and turned them into stem cells, which can grow into any type of cell to build or repair different parts of the body. Professor Kurian's team, with work led by Dr. Serena Barral, converted these stem cells into the exact brain cells (dopaminergic neurons) that carry the genetic 'fault' responsible for DTDS.

Using this laboratory model—or 'disease in a dish' - made directly from the cells of children with this rare condition, scientists were able to test the experimental gene therapy for DTDS and show that it could relieve the disease-related defects in DTDS brain cells.

The team used fluorescence microscopy to see what was happening in their 'disease in a dish'. The seemingly random pattern of colours in the untreated cells (left) shows how the neurons and their communicating 'arms' - called neurites—had not formed properly in cells with DTDS. The gene therapy treated cells form a much more obvious cluster pattern for the neuron—seen in white—with its red neurites, essentially showing the DTDS is cured in a laboratory model.

A further collaboration with UCL's Professor Simon Waddington and Dr. Joanne Ng enabled the researchers to build on their 'disease in a dish'

results, studying DTDS in mice and testing gene therapy as a cure. The gene therapy injects a modified, harmless virus containing the healthy gene into the area of the brain where this gene is missing. The mice were successfully cured of their symptoms including involuntary and disordered movements, progressive parkinsonism and weightloss. Based on the promising results of the laboratory tests, the next phase is to develop a clinicaltrial which would involve children diagnosed with DTDS.

22-year-old Shannon from Cornwall was one of the first patients diagnosed with DTDS after Professor Kurian discovered the faulty gene in 2009. Her mum, Judith said: "Shannon is a happy, bubbly girl and finds everything hilarious. DTDS meant Shannon suffered badly from shakes—she couldn't control her legs. She shakes very slightly now, but it's very mild."

On Shannon being one of the first patients in whom the faulty gene was discovered, Judith said, "It's amazing. The last time we saw Professor Kurian she said there had been a breakthrough with the research, but it hadn't been tried on anyone yet.

"GOSH is a brilliant hospital and I donate to the charity every month to help keep the extra support at the hospital going."

Professor Manju Kurian, Consultant Paediatric Neurologist at GOSH and NIHR Research Professor at UCL Great Ormond Street Hospital Institute of Child Health, co-lead author on this study and the scientist behind the discovery of this disease: "Our study provides real hope of an effective treatment for children who are living with this devastating, life-limiting brain disease, and it is hugely exciting to be at the stage of planning a clinical trial just ten years after discovering the gene that causes the condition.

"We hope this pioneering gene therapy will prevent the progression of this rare but cruel disease with a single procedure, giving children the improved quality and length of life that they deserve. If we can use gene therapy to treat children with this condition early enough, there is great potential for improvement in their health.

"We're hugely grateful to our funders including GOSH Charity who supported our research at the very beginning, as well as the Wellcome Trust, MRC, John Black Charitable Foundation, Robert Luff Foundation and Rosetrees for their investment; without their support we wouldn't be within touching distance of delivering a breakthrough cure that these children so desperately need."

Professor Simon Waddington, Professor of Gene Therapy at UCL, co-lead author on this study:

"Our whole working process has been guided by one principle: we want to find the answers for these children and how we can treat them. "The mice received the same carefully selected vector and delivery route that we plan to use intreating the children. This careful selection has allowed us to progress rapidly to design a protocol so we can start the clinical trial next year.

"While DTDS is rare, we know that there are many other conditions we can model in this way, opening the door for a standardised approach to finding cures for these rare conditions."

Dr. Kiki Syrad, Director of Grants and Impact at GOSH Charity, which provided funding early in the development of this treatment said: "At GOSH Charity we fund paediatric research to aid the discovery of desperately needed new treatments and cures for children living with rare diseases.

"We are absolutely delighted to see the progress that this study publication points to. It offers the hope of an effective treatment which could be nothing short of lifechanging for children and families living this with this rare, devastating condition. This is the hope that paediatric rare disease research can offer, and that's why we will continue to invest in trail-blazing projects such as this."

More information: Joanne Ng et al, Gene therapy restores dopamine transporter expression and ameliorates pathology in iPSC and mouse models of infantile parkinsonism, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.aaw1564

Provided by University College London

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