Early results of gene therapy trial for 'childhood dementia' show promise

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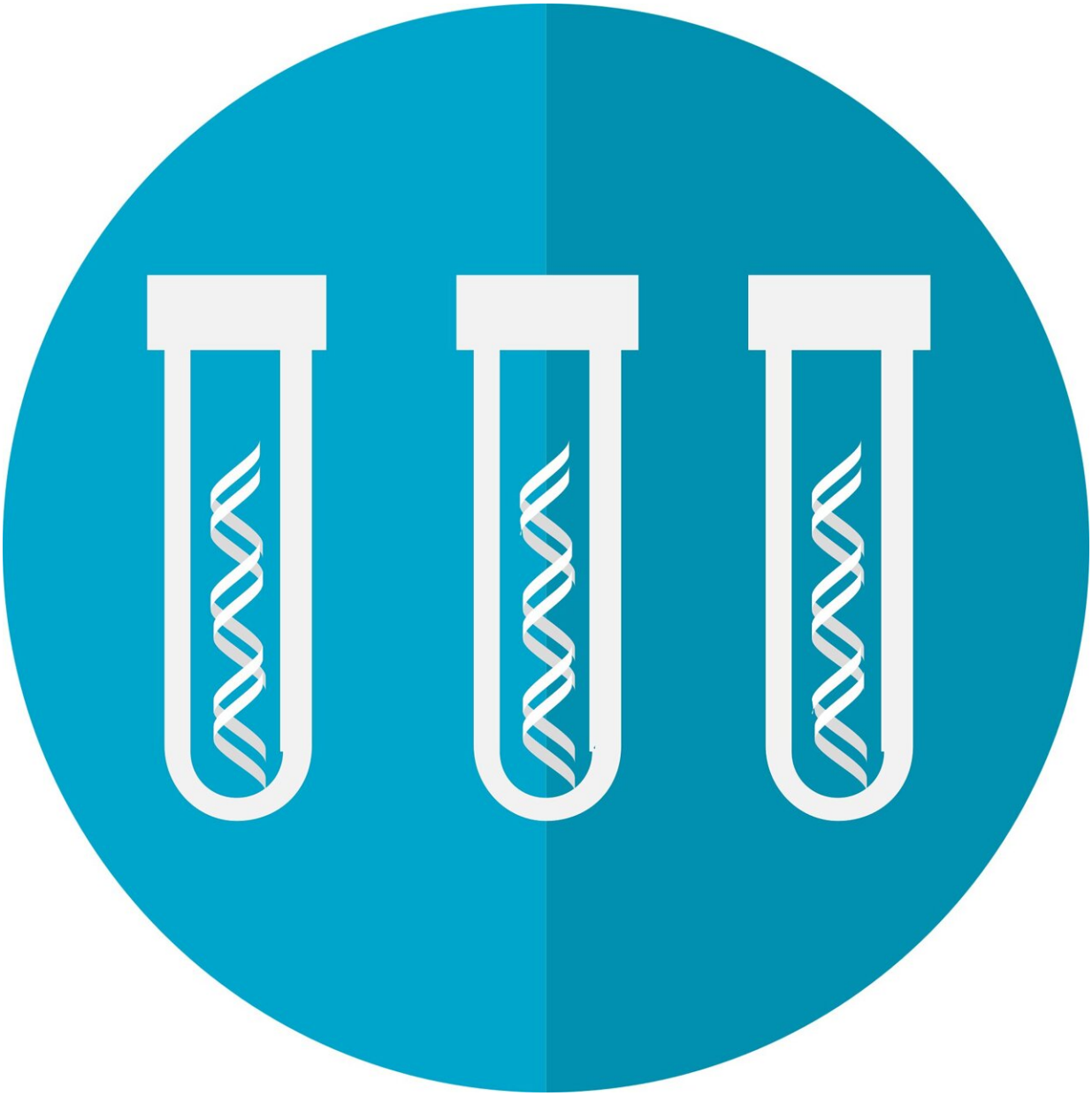

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Researchers will tell an international conference today (Feb. 24) that an investigational gene therapy for Sanfilippo syndrome—which leads to a form of childhood dementia—has shown promising early results in a proof-of-concept study.

It found four out of five patients diagnosed with Sanfilippo have continued to gain cognitive skills in line with development in healthy children after being given the investigational gene therapy, OTL-201.

However, the researchers urge caution as the majority of patients have not reached the age of 4–5 years where the most severe stages of disease progression typically present.

The trial patients were six to 24 months of age at the time of administration of OTL-201, and the preliminary results are based on a median follow-up of two years (range: nine to 30 months).

Patients enrolled in the trial will be followed for a minimum of 36 months during which time the study investigators will continue to report additional biochemical and clinical outcomes.

The rare genetic metabolism disorder called Sanfilippo syndrome Type A- or Mucopolysaccharidosis Type IIIA (MPS-IIIA)- is a genetic disease with devastating effects on the central nervous system affecting around 1 in 70,000 children.

Patients with MPS-IIIA have a mutation in the SGSH gene, causing them to lack an enzyme which normally breaks down large sugar molecules.

These molecules then accumulate in the cells of the body causing irreparable damage to many organs including the brain, leading to inflammation and damage to brain tissue.

The investigational gene therapy OTL-201 works by collecting a patient's own blood stem cells and inserting a working copy of the SGSH gene using a modified virus, known as a lentiviral vector.

The patient's modified blood stem cells, now including a working copy of the SGSH gene, are then given back to the patient.

This enables patients to then make this missing SGSH enzyme and provide it throughout the body from blood cells made in the bone marrow. These stem cells can make monocytes, which are specialized blood cells able to enter the brain. This means they can release SGSH enzyme to potentially help stop damage to the brain.

The results showed:

- An improvement in neurocognitive assessments compared with natural progression of the disease in one of the children at 18-months post-treatment.
- Three additional patients are currently within the normal cognitive development range at nine to 18 months post-treatment, but require longer follow-up to assess outcomes.
- After a median of two years, OTL-201 which was generally well tolerated in all the patients, achieved sustained engraftment in the bone marrow.
- Higher amounts of the SGSH enzyme were seen than would be normally found in the blood and cerebrospinal fluid of healthy children.

Six serious adverse events (SAEs) have been reported in patients in the

study and were considered to be caused by procedures required for the administration of OTL-201 or background disease. No SAEs were considered related to OTL-201 and no fatal cases have been reported, to date.

Professor Brian Bigger, Chair in Cell and Gene Therapy at the University of Manchester, who carried out the preclinical work said, "We have been hopeful this therapy will be transformative for patients- and these early results are very encouraging—but there's still a long way to go."

"Importantly, the safety profile of the investigational therapy is currently considered favorable in these patients, with the lentiviral vector reporting a polyclonal pattern of integration, and blood stem cells engrafting and producing cells in the blood system which are able to make the missing enzyme in patients.

"The human monocyte-specific promoter in the lentiviral vector was designed to have a very low risk of causing insertional mutagenesis—the accidental switching on of genes causing cancer. This is critical for the future safety of the patients and the developmental potential of this therapy."

Professor Robert Wynn, Chief Investigator on the trial at The Royal Manchester Children's Hospital, part of Manchester University NHS Foundation Trust (MFT) said, "These are encouraging results for children living with MPS-IIIA and their families, who currently have no effective treatment options."

"In addition to sustained engraftment of gene-corrected cells and supraphysiological SGSH enzyme levels in the periphery, the early neurocognitive findings show most patients are gaining skills in line with the development of healthy children. In one patient, we also have seen a

marked improvement from disease natural history, and we hope to see similar results in the other patients with longer follow-up."

Professor Simon Jones, Consultant in Pediatric Inherited Metabolic Disease at the Manchester Center for Genomic Medicine at Saint Mary's Hospital and Clinical Director of NIHR Manchester Clinical Research Facility at Royal Manchester Children's Hospital, said, "There are currently no other treatment options for children with MPS-IIIA. We hope this therapy will have a positive impact on the lives of our children and their families, improving the symptoms of this devastating disease."

Leslie Meltzer, Ph.D., chief medical officer of Orchard Therapeutics said, "These promising early findings continue to show the ability of our HSC gene therapy platform to enable the migration of gene-corrected cells into the central nervous system and the localized delivery of therapeutic enzymes and proteins to the brain to potentially correct neurodegeneration in multiple severe conditions, building on our programs in neurometabolic disorders."

"While these early results are encouraging, longer follow up is needed, as the majority of the patients in this trial have not reached the age where the most severe stages of disease progression typically manifest. We are working with our collaborators at The University of Manchester and Royal Manchester Children's Hospital to continue following patients in this ongoing study and more fully characterize the clinical and safety profile of OTL-201."

The results were presented at the WORLD Symposium2023 on Lysosomal Diseases on February 24.

Provided by University of Manchester