Family guide to understanding Lysogene's gene therapy approach for MPS IIIA

Lysogene's gene therapy is an experimental new therapy that targets the cause of mucopolysaccharidosis IIIA (MPS IIIA), also known as Sanfilippo type A syndrome.

Children with MPS IIIA do not produce enough enzyme activity to break down a substance in the body called heparan sulfate.

As heparan sulfate accumulates, it affects the normal functions of the body and in particular the brain.

The lack of enzyme activity is due to a defective gene that would normally instruct the cells of the body to make a functional enzyme.

The gene in question is called N-sulfoglucosamine sulfohydrolase (SGSH).

WHAT IS GENE THERAPY?

Gene therapy is an experimental technique that uses genes to treat or prevent disease. In MPS IIIA we are replacing the faulty SGSH gene with a healthy copy of the gene. By replacing the defective gene it is hoped that the body will start making sufficient quantities of enzyme and therefore slow or halt the progression of the disease.

In order to get the healthy copy of the gene to where it needs to be in the body, a virus is used as a carrier. The virus is made harmless by removing its own genes (those that would cause a viral infection) and replacing them with the SGSH gene. Different viruses are able to enter different cells in the body. The AAVrh10 virus, used by Lysogene, has been chosen for gene therapy in MPS IIIA because it is particularly good at spreading in the brain. Studies have shown that cells treated with this gene therapy are able to produce the missing enzyme[1].

HOW IS IT GIVEN?

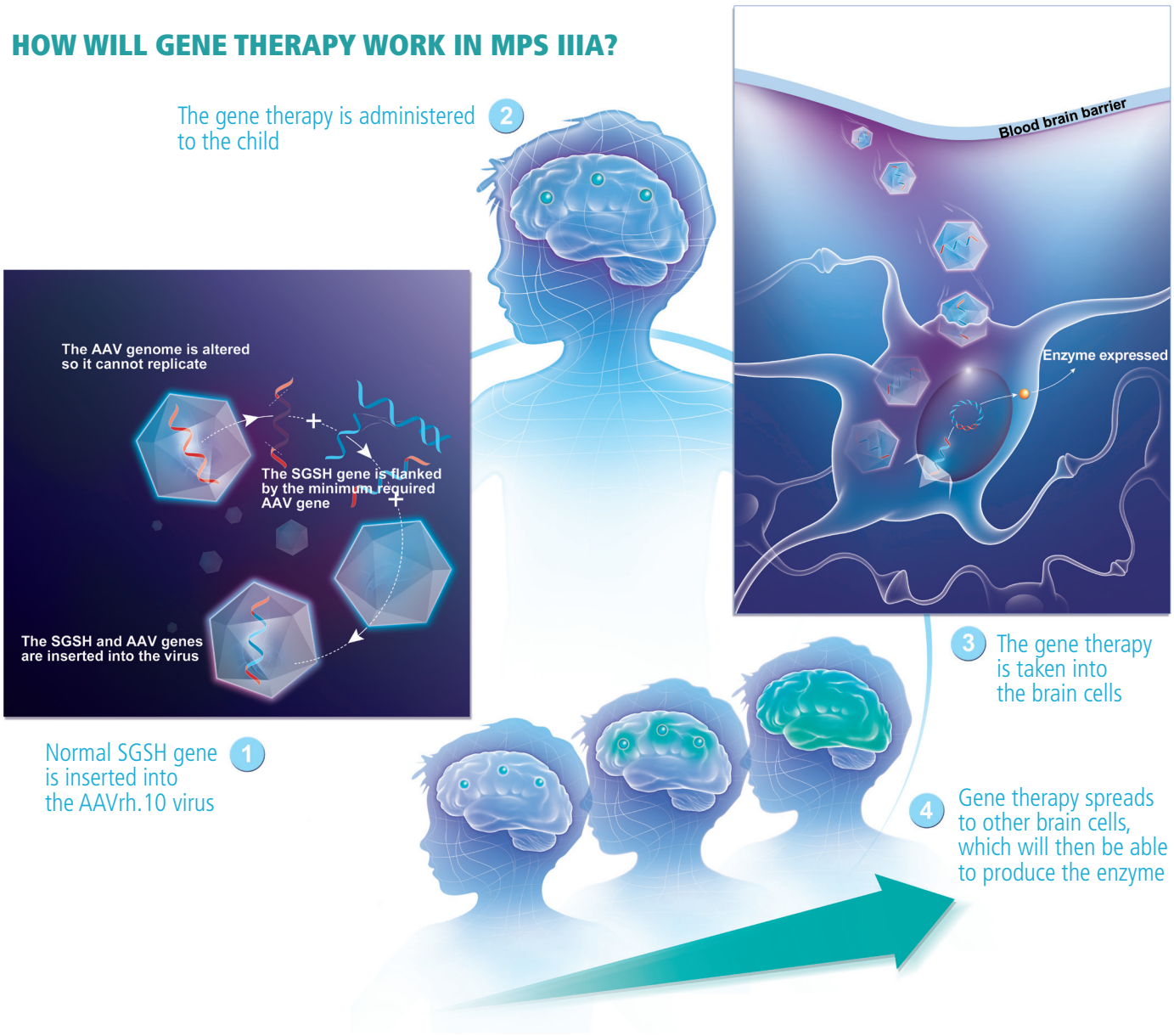
The best way to deliver this gene therapy, to limit the damaging effects of MPS IIIA on the brain, is to administer it directly to the brain via injection[2]. This is because our brains are protected by what is known as the 'blood-brain barrier.' This stops unwanted substances in the blood from entering the brain and would restrict the newly produced enzyme from entering the brain if gene therapy was given by normal injection. For this reason, the gene therapy is given by a surgeon under general anesthesia, and is then able to initiate the production of enzyme and limit the neurological effects of the disease on the brain.

HAS GENE THERAPY, DIRECT TO THE BRAIN, ALREADY BEEN TESTED IN MPS IIIA?

Lysogene has completed a phase I/II clinical study[3] in four children with MPS IIIA. The results of this study have been reported by Professor Tardieu in the Journal of Human Gene Therapy[4]. To date, the children have been monitored for four years following treatment. No significant risk has been associated with the injection or with the long-term presence of the gene therapy. Similar treatments have also been used in different diseases on small numbers of children without problems. Gene therapy delivered directly to the brain has also been studied in more common diseases such as brain tumors, Alzheimer's disease, Parkinson's disease and Huntington's disease[5].

Lysogene is currently planning another clinical trial, with a next generation gene therapy product and more details will be made available in due course.

HOW WILL GENE THERAPY WORK IN MPS IIIA?



WHEN CAN WE EXPECT TO SEE POSSIBLE CHANGES AFTER THE GENE THERAPY ADMINISTRATION?

It is hoped that the gene therapy will stop the progression of the disease in a child receiving treatment. Children will be monitored very closely by means of examinations, about every six months, allowing us to assess the nervous system through neurocognitive tests and brain imaging.

WILL THE GENE THERAPY NEED TO BE REPEATED?

Gene therapy is intended to be a one-time treatment. We know, from pre-clinical experiments in non-human primates that when enzyme is present in the brain the diseased brain cells return to normal function i.e. they break down heparan sulfate. This effect is very long-lasting, more than eight years[6], but we don't know yet whether it is "for life".

[1] Winner LK, Beard H, Hassiotis S et al. A pre-clinical study evaluating AAVrh10-based gene therapy for Sanfilippo syndrome. Hum Gene Ther 2016.
[2] Rosenberg JB, Sondhi D, Rubin DG et al. Comparative Efficacy and Safety of Multiple Routes of Direct CNS Administration of Adeno-Associated Virus Gene Transfer Vector Serotype rh.10 Expressing the Human Arylsulfatase A cDNA to Nonhuman Primates. Hum Gene Ther Clin Dev 2014;25:164-177.
[3] For more information about clinical trials in general, please see ClinicalTrials.gov – clinical trial phases.
[4] Tardieu M, Zérah M, Husson B, et al. Human Gene Therapy. 2014 Jun;25(6):506-16.
[5] Hocquemiller M, Giersch L, et al. AAV based gene therapy for CNS diseases. Hum Gene Ther. 2016 Jun 7.
[6] Hadaczek P, Eberling JL, Pivirotto P et al. Eight years of clinical improvement in MPTP-lesioned primates after gene therapy with AAV2-hAADC. Mol Ther 2010;18:1458-1461.

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