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Attacking a rare disease at its source with gene therapy

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Treating the rare disease MPS I is a challenge. MPS I, caused by the deficiency of a key enzyme called IDUA, eventually leads to the abnormal accumulation of certain molecules and cell death.

The two main treatments for MPS I are bone marrow transplantation and intravenous enzyme replacement therapy, but these are only marginally effective or clinically impractical, especially when the disease strikes the central nervous system (CNS). Using an animal model, a team from the Perelman School of Medicine at the University of Pennsylvania has proven the efficacy of a more elegant way to restore IDUA levels in the body through direct gene transfer. Their work was published this week online in *Molecular Therapy*.

"The study provides a strong proof-of-principle for the efficacy and practicality of intrathecal delivery of gene therapy for MPS patients," said lead author James M. Wilson, MD, PhD, professor of Pathology and Laboratory Medicine and director of the Penn Gene Therapy Program. "This first demonstration will pave the way for gene therapies to be translated into the clinic for lysosomal storage diseases."

This family of diseases comprises about 50 rare inherited disorders marked by defects in the lysosomes, compartments within cells filled with enzymes to digest large molecules. If one of these enzymes is mutated, molecules that would normally be degraded by the lysosome accumulate within the cell and their fragments are not recycled. Many of the MPS disorders can share symptoms, such as speech and hearing

problems, hernias, and heart problems. Patient groups estimate that in the United States 1 in 25,000 births will result in some form of MPS. Life expectancy varies significantly for people with MPS I. Individuals with the most severe form rarely live more than 10 years.

The team used an adeno-associated viral (AAV) vector to introduce normal IDUA to glial and neuronal cells of the brain and spinal cord in a feline model. Their aim was to treat the CNS manifestations of MPS at the source. After a single injection of the AAV9 vector expressing a normal feline IDUA gene sequence and various promoters, the investigators collected blood serum and cerebrospinal fluid (CSF) samples from the test animals and from untreated controls

Some of the treated animals displayed a sharp decline in IDUA levels in the CSF after an initial elevation in the enzyme, which the researchers attribute to an antibody response against IDUA. However, IDUA still persisted at a level sufficient to elicit a positive therapeutic response.

The team also found that one CSF enzyme was elevated in the presence of MPS and propose it could be used as a biomarker for disease activity. All the treated animals displayed a marked decrease in this enzyme, confirming a definite biochemical response to the introduction of the gene vector.

Tissue samples from the brain and spinal cord showed widespread presence of the AAV9 vector throughout all regions of the CNS. IDUA deficiency in the CNS caused by MPS1 results in the accumulation of cholesterol and lipids called gangliosides in brain tissue and accumulation of the sugar glycosaminoglycan in connective tissue and cerebral blood vessels. The animals treated with the AAV9-IDUA vector displayed an almost complete reversal of these molecular markers of MPS.

"Signs of MPS were also virtually completely corrected in the liver and spleen," notes Wilson.

Even with a possible antibody response, conclude the researchers, a single injection nearly reversed all evidence of MPS pathology in the CNS of the treated animals. Next steps could include possible human trials and the expansion of this therapeutic approach to other lysosomal diseases that attack CNS cells.

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