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Liver gene therapy corrects heart symptoms in model of rare enzyme disorder

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In the second of two papers outlining new gene-therapy approaches to treat a rare disease called MPS I, researchers from Perelman School of Medicine at the University of Pennsylvania examined systemic delivery of a vector to replace the enzyme IDUA, which is deficient in patients with this disorder. The second paper, which is published online in the *Proceedings of the National Academy of Sciences* this week, describes how an injection of a vector expressing the IDUA enzyme to the liver can prevent most of the systemic manifestations of the disease, including those found in the heart.

The first paper, published in *Molecular Therapy*, describes the use of an adeno-associated viral (AAV) vector to introduce normal IDUA to glial and neuronal cells in the brain and spinal cord in a feline model. The aim of that study was to directly treat the central nervous system manifestations of MPS while the more recent study aims to treat all other manifestations of the disease outside of the nervous system.

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.

The two main treatments for MPS I are bone marrow transplantation and intravenous enzyme replacement therapy (ERT), but these are only marginally effective or clinically impractical, and have significant drawbacks for patient safety and quality of life and do not effectively address some of the most critical clinical symptoms, such as life-threatening cardiac valve impairments.

"Both of these papers are the first proof-of-principle demonstrations for the efficacy and practicality for gene therapies to be translated into the clinic for lysosomal storage diseases," says lead author James M. Wilson, MD, PhD, professor of Pathology and Laboratory Medicine and director of the Penn Gene Therapy Program. "This approach may likely turn out to be better than ERT and compete with or replace ERT. We are especially excited about the use of this approach in treating the many MPS I patients who do not have access to ERT due to cost or inadequate health delivery systems to support repeated protein infusions, such as in China, Eastern Europe, India, and parts of South America."

Patients with mucopolysaccharidosis type I (MPS I), accumulate compounds called glycosaminoglycans in tissues, with resulting diverse clinical symptoms, including neurological, eye, skeletal, and cardiac disease.

Using a naturally occurring feline model of MPS I, the team tested liver-directed gene therapy via a single intravenous infusion as a means of establishing long-term systemic IDUA presence throughout the body.

The team treated four MPS I cats at three to five months of age with an AAV serotype 8 vector expressing feline IDUA. "We observed sustained serum enzyme activity for six months at approximately 30 percent of normal levels in one animal and in excess of normal levels in the other three animals," says Wilson.

Remarkably, treated animals not only demonstrated reductions in glycosaminoglycans storage in most tissues, but most also exhibited complete resolution of aortic valve lesions, an effect which has not been previously observed in this animal model or in MPS I patients treated with current therapies.

Critical to the evaluation of these novel therapies is the feline model of MPS I, which was provided through coauthor Mark E. Haskins, School of Veterinary Medicine at Penn. Haskins and his colleagues maintain a variety of canine and feline models of human genetic diseases that have been instrumental in establishing proof of concept for a number of novel therapeutics, including the current enzyme replacement therapy.

The Penn team says that these findings point to clinically meaningful benefits of the robust enzyme expression achieved with liver gene transfer that may extend the economic and quality of life advantages over lifelong enzyme infusion.

More information: Liver-directed gene therapy corrects cardiovascular lesions in feline mucopolysaccharidosis type I , *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1413645111

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