Gene therapy for pompe disease effective in mice, poised for human trials

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After decades investigating a rare, life-threatening condition that cripples the muscles, Duke Health researchers have developed a gene therapy they hope could enhance or even replace the only FDA-approved treatment currently available to patients.

The gene therapy, demonstrated in mice, is described in a new study

published online in the journal *Molecular Therapy - Methods & Clinical Development*. The therapy uses a modified virus to deliver a gene to the liver where it produces GAA, an enzyme missing in people with Pompe disease.

Study authors have received approval from the FDA to launch a Phase 1 clinical trial in humans and are currently working to secure funding.

Pompe disease is an inherited condition that affects approximately 1 in 20,000 babies and can also appear in adulthood. People with the condition lack the enzyme GAA, which means their bodies can't metabolize the sugar, glycogen. As a result, glycogen builds up in the muscles. In babies, this leads to improper muscle development and, if undiagnosed and untreated, can lead to respiratory problems, heart failure and death.

"The outlook for Pompe disease is much improved since enzyme replacement has become available—it can reverse involvement of the heart and prolong survival," said senior author Dwight Koeberl, M.D., Ph.D., professor of pediatrics and a medical genetics specialist at Duke.

"But not everyone responds to this treatment," Koeberl said. "Many patients make some antibodies, and this can really interfere with treatment. Some infants still die from Pompe disease. Others have to add immune suppression to their treatment, which can lead to other complications. Gene therapy could help these patients."

The Duke-led research team found that a single small dose of gene therapy was as effective as enzyme replacement therapy (ERT) in clearing the buildup of glycogen from the muscles in mice. A larger dose offered superior results to ERT. A single treatment spurred the liver to continuously produce GAA without additional treatment, the study authors said. Enzyme therapy requires infusions once or twice a month

to lower glycogen levels in the muscles.

Unlike ERT, the gene therapy doesn't trigger an immune response, a reaction that can limit successful treatment in about half of babies with Pompe. In fact, the gene therapy appeared to reverse immune responses in mice that had previously developed antibodies in response to enzyme replacement, Koeberl said.

The gene therapy uses an inactivated form of adeno-associated virus (AAV), which does not cause illness and has been used as a delivery system for hemophilia B and muscular dystrophy treatments, among others, Koeberl said.

The emerging gene therapy is just the latest development for a team of scientists at Duke that has been working for three decades to study the causes and potential treatments for glycogen-storage diseases and specifically Pompe.

"When we enter our careers in the field of genetics, we are faced with the many unmet needs for patients with rare diseases," said Priya Kishnani, M.D., chief of the medical genetics division at the Duke University School of Medicine. "Before enzyme replacement became available in 2006 for Pompe disease, we would continue to give parents bad news—take your beautiful baby home; he or she will die within their first year of life. I knew we had to do something about this."

Kishnani has researched Pompe for 25 years, beginning under prominent geneticist Y.T. Chen, the previous chief of the medical genetics division at Duke. In the 1990s and 2000s, Chen and Kishnani worked with biotech firm Genzyme to develop ERT and lead clinical trials.

Since then, Kishnani and dozens of other Duke physicians have been national leaders in Pompe disease, continuing to research the condition,

improve the delivery of ERT, manage immune responses to the drug and improve genetic counseling for families.

The Duke team has helped develop a blood test to diagnose Pompe and a biomarker to monitor severity of the disease and patients' response to treatment. For nearly 10 years, Kishnani has led a group of physicians to advocate nationally for universal newborn screening, which became a formal recommendation of the U.S. Department of Health and Human Services in 2015. The team's next step is to develop small molecule or oral drugs that could suppress the buildup of glycogen in the muscles.

"There's a rich heritage of expertise on glycogen storage disease at Duke, spanning about 40 years," Kishnani said. "We have continued to grow from the era of cloning the genes to developing animal models, to collaborating with pharma to conduct clinical trials here at Duke. I think we have come full circle, from bench to bedside and back to the bench in every aspect of the disease."

More information: Sang-oh Han et al, Low-dose liver targeted gene therapy for Pompe disease enhances therapeutic efficacy of ERT via immune tolerance induction, *Molecular Therapy - Methods & Clinical Development* (2017). DOI: 10.1016/j.omtm.2016.12.010

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