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Gene therapy could save kids from a lifetime of eating cornstarch

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A gene therapy treatment that restores a missing liver enzyme in test animals could provide a cure for a rare metabolic disorder in humans, according to Duke University Medical Center researchers.

People born with the disorder, called glycogen storage disease type Ia (GSD-Ia), can't make an enzyme that helps the liver store and release glucose, the sugar that all cells use for energy. Without treatment, their blood sugar levels drop dangerously low, causing seizures and organ damage. Eating raw cornstarch, a slowly digested carbohydrate, and avoiding dietary sugar can help people with GSD-Ia maintain their glucose levels. However, even a special diet does not prevent the eventual liver damage that results from the absent enzyme, and many adults with the disease develop liver and kidney failure or liver cancer. With treatment, most people with GSD-1a have a relatively normal lifespan.

The gene therapy developed at Duke would give liver cells the correct genetic code for manufacturing the enzyme. A modified virus transfers the enzyme genes by infecting liver cells. The virus is not linked to any known human disease, and cannot copy itself and spread to other people, said medical geneticist Dwight Koeberl, M.D., Ph.D., lead study author and an associate professor in the Department of Pediatrics.

The research involved creating a virus so focused on targeting liver cells that only a tiny amount is needed for treatment, minimizing potential side effects. Showing that the virus is safe and effective in small doses is

an important step in bringing the treatment to clinical trials in humans.

The gene therapy replaced the missing enzyme in the liver to fully normal levels, and protected both mice and dogs with the disease from low blood glucose for up to a year. “No one has fully corrected the enzyme that produces glucose in the liver before. We think we can correct every cell in the liver,” Koeberl said.

The results appear in the March 11 2008 issue of the journal *Molecular Therapy*. The research was funded by the Children's Fund for GSD Research, the Association for Glycogen Storage Disease and the Duke Children’s Miracle Network. Dr. Emory and Mrs. Mary Chapman, and Dr. and Mrs. John Kelly, families of a child with GSD-Ia, also provided support.

The researchers tested the technique on mice bred without the genetic code to make the enzyme, as well as young dogs with a naturally-occurring canine form of glycogen storage disease. The original genetic carrier, a Maltese, was identified by a Georgia breeder, and veterinarians at North Carolina State University College of Veterinary Medicine have worked with Duke to maintain a population of dogs with the disease since the mid-1990s.

The success of the new treatment makes the therapy worth testing in long-term animal studies, Koeberl said. “This is a step along the way toward developing a curative therapy for our patients,” he said. The key is finding funding for a years-long trial. “There are not a lot of companies developing treatments for rare diseases,” he added.

GSD-Ia occurs in about one of every 100,000 births in the U.S. Duke is treating about 100 patients with the disease.

A long-term study would demonstrate whether gene therapy can prevent

complications such as kidney failure and liver cancer, which develop even if people strictly control their diet and blood sugar levels. Other problems associated with the disease include growth restriction, high blood pressure, pancreatitis and persistent hypoglycemia.

“There are definite well-documented limitations to the dietary therapy. People can’t just follow a diet and count on living full, healthy lives,” Koeberl said.

Lengthy trials are also necessary because the corrected genes don’t transfer when liver cells divide and copy themselves. However, the slow rate at which liver cells divide means the treatment may be effective for many years, with only a few boosters needed during an individual’s lifetime, Koeberl said.

Source: Duke University