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Researchers identify way to increase gene therapy success

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Scientists in The Research Institute at Nationwide Children's Hospital have found a way to overcome one of the biggest obstacles to using viruses to deliver therapeutic genes: how to keep the immune system from neutralizing the virus before it can deliver its genetic payload. In a study published recently in *Molecular Therapy*, researchers found that giving subjects a treatment to temporarily rid the body of antibodies provides the virus safe passage to targeted cells, allowing it to release a corrective or replacement gene to treat disease.

Gene therapy is among the most promising treatment options for such genetic disorders as muscular dystrophy, congenital blindness and hemophilia. Scientists also are investigating gene therapy as a cure for some cancers, neurodegenerative diseases, viral infections and other acquired illnesses. To get the therapeutic gene into cells, researchers have turned to viruses, which deliver their genetic material into cells as part of their normal replication process. Time and time again, these efforts have been thwarted by the body's own immune system, which attacks the viral vector. The therapeutic genes aren't delivered and disease rages on.

Now, a team led by Louis G. Chicoine, MD, Louise Rodino-Klapac, PhD, and Jerry R. Mendell, MD, principal investigators in the Center for Gene Therapy at Nationwide Children's, has shown for the first time that using a process called plasmapheresis just before delivering a virus-packed gene therapy protects the virus long enough for it to enter the cell and deliver the gene.

Plasmapheresis, widely used to treat patients with autoimmune disorders, removes blood from the body, separates the plasma and cells, filters out antibodies, and returns the blood to the patient. The antibody loss is temporary; the body begins producing new antibodies within a few hours of the procedure.

In a study of a gene therapy designed to treat Duchenne muscular dystrophy (DMD), Drs. Chicoine and Rodino-Klapac used plasmapheresis in a large animal model, then injected a virus packed with a micro-dystrophin gene. When they examined the levels of micro-dystrophin gene expression in the animals, they found a 500 percent percent increase over gene expression in animals that did not receive plasmapheresis. Dr. Mendell, director of the Center for Gene Therapy, helped conceive of this treatment for DMD patients based on experience with autoimmune diseases such as myasthenia gravis and inflammatory nerve diseases.

"Right now, gene therapy seems to work best in patients who have no antibodies for the virus being used to deliver the gene," Dr. Mendell says. "That limits the number of patients who can benefit from gene therapy."

Using plasmapheresis would increase the potential for gene therapy, Dr. Chicoine adds, by eliminating one obstacle of immune reaction.

"As gene therapy becomes more prevalent, patients may need to receive more than one treatment," Dr. Rodino-Klapac says. "The problem is that when they get the first treatment, their body will develop antibodies to the virus used to deliver the gene. Using plasmapheresis on someone who previously received gene therapy could allow them to be treated again."

More information: L. G. Chicoine, C. L. Montgomery, W. G.

Bremer, K. M. Shontz, D. A. Griffin, K. N. Heller, S. Lewis, V. Malik, W.E. Grose, C. J. Shilling, K. J. Campbell, T. J. Preston, B. D. Coley, P. T. Martin, C. M. Walker, K. R. Clark, Z. Sahenk, J. R. Mendell, and L. R. Rodino-Klapac, Plasmapheresis eliminates the negative impact of AAV antibodies on micro-dystrophin gene expression following vascular delivery. *Molecular Therapy*. Epub 2013 Oct 23. DOI: 10.1038/mt.2013.244