Gene Therapy 101

An overview of the field of study and its emerging application as a treatment for Lafora disease.

RESEARCH SIMPLIFIED BY

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QUESTIONS?

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Additional reading: https://patienteducation.asgct.org/gene-therapy-101

WHAT IS IT?

Gene Therapy is the use of genetic material (DNA or RNA) to alter the production of a specific protein in your body. It can be used to make a correct version of a missing protein, or it can be used to decrease the activity of a specific protein by reducing production of that protein.

HOW DOES GENE THERAPY WORK?

Most commonly, gene therapy uses something called a "viral vector" to deliver genetic material to your cells. Viral vectors are a good delivery system for the therapy because they already have a good mechanism for getting into the cells in your body. To ensure these viral vectors are safe, the viral genetic material is removed and replaced with the new genetic material for treating the disease. Sound complicated? Here's an easy way to think about it:

Imagine a package being shipped to your house. The viral vector is like the box – it is a durable container for transporting DNA or RNA. The label on the box ensures it gets to the right house. In your body, the type of viral vector you use contains its own sort of "shipping label" to make sure it reaches the right cells in your body. Once the package reaches your home, you bring it inside and then take out the contents. The same thing happens in your cells – they recognize the shipping label and take the vector inside. Once the viral vector is inside the cell, the package is opened, and the contents are released to begin treatment.

One common type of viral vector is called Adeno-associated Virus (AAV). This is a good-sized package for small DNA or RNA deliveries. There are many different sub-types of AAV vectors that can target specific cell types. AAV9 is a vector capable of targeting neurons, making it a good delivery system for gene therapy in neurological disorders.

HOW OFTEN DO YOU NEED TREATMENT WITH AAV THERAPIES?

That depends on the type of cell in your body that you need to target. Because we took the viral genetic material out of the viral vector, it cannot replicate when a cell divides. That means that for cells that divide rapidly, like liver cells, new cell growth would quickly dilute the number of treated cells. However, in the nervous system, where cells divide much more slowly, the treated cells can last for years. This means that you could potentially need just one life-time dose of the AAV therapy.

WILL THIS TREATMENT WORK FOR EVERYONE?

No. One problem with AAV therapy is natural immunity. When a viral vector enters your body, your body recognizes it as foreign material and starts to make antibodies to destroy the vector and fight off infection. Your immune system then makes a record of that viral vector so it can quickly fight infection from that virus in the future. It cannot tell the difference between a harmful AAV and one that has been modified for gene therapy – the package looks the same on the outside. So, if you have already been infected with an AAV at some point in your life (about 30% of the population), then your body may attack and destroy the package before it reaches your cells.

Scientists are working on ways to overcome the problem of natural immunity, but for now, there will be some patients where the therapy would not work.

HAVE ANY AAV THERAPIES BEEN APPROVED BY THE FDA?

None for treating Lafora Disease, but two AAV therapies have been approved by the FDA for other neurological diseases: Zolgensma, a gene therapy to treat spinal muscular dystrophy, and Luxturna, a gene therapy for Leber congenital amaurosis.

HOW SOON COULD AAVS BE USED TO TREAT LAFORA DISEASE?

Gene therapy development is still in the early pre-clinical stages for Lafora Disease. On average, it takes five to seven years to complete all pre-clinical data in mouse and non-human animal models needed for advancing to clinical trials, and the clinical trial process for FDA approval takes on average an additional five to seven years.

We are still a long way from being able to use gene therapy to treat Lafora Disease, however, gene therapy is an important step toward curing Lafora Disease for future generations. Recently, there have been several publications discussing the development of gene therapy to treat Lafora Disease.

REDUCING GLYCOGEN SYNTHESIS

Lafora Body (LB) accumulation drives disease progression in Lafora Disease. These LBs are aggregates of misshapen and excessive glycogen. Dr. Berge Minassian's lab has developed and tested an AAV gene therapy for Lafora Disease to reduce glycogen synthesis and halt Lafora Body aggregation in mice. The AAV reduces the production of Glycogen Synthase (GYS1), the protein responsible for synthesizing glycogen in the brain.

Check out the results of that study: https://link.springer.com/article/10.1007/s13311-022-01218-7

MALIN RESTORATION

Patients with Lafora Disease have lost the function of either the protein malin or laforin. Dr. Jordi Duran's lab recently published a paper showing that restoring malin expression in a mouse model that lacks malin can reduce Lafora Body accumulation and neuroinflammation. This proof-of-concept suggests that it would be beneficial to develop gene therapy for restoring malin expression in patients where malin is mutated or missing.

Check out the results of his experiment: https://academic.oup.com/braincomms/advance-article/doi/10.1093/braincomms/fcac168/6615062