

Gene Therapy to Cure Parkinson's Disease: A New Solution on the Horizon?

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As modern science and technology continue to advance, a new potential solution for curing diseases has begun to receive attention: gene therapy. Although the term includes the word “therapy”, it is far from the psychology-based therapy methods that we may be more familiar with. Gene therapy is a method that can alter a person’s genes to treat or cure diseases. Applications include replacing disease-causing genes with their healthier copies, inactivating disease causing genes that are not performing their roles properly, and even introducing new or modified genes to treat diseases (Center for Biologics Evaluation and Research, 2020). Products of gene therapy can be administered as nucleic acids, viruses, or genetically engineered microorganisms, and they can, in theory, be used to influence future generations through germ cells (sperm and egg cells). This is called germline gene therapy, and it is currently prohibited by the U.S. federal government due to its ethical concerns (Wirth et al., 2013). This article will discuss the less controversial somatic gene therapy, which involves inserting genetic material into specific target cells, thus ensuring that future generations are not affected. The applications of gene therapy are still in the experimental phase and haven’t quite left the research laboratories, but, as will be discussed, somatic gene therapy has potential to be a treatment for neurodegenerative diseases, especially Parkinson’s Disease.

Some people are born with a mutated gene that causes an essential protein to be either missing or broken. In such cases, gene therapy could help restore the protein’s function by introducing a normal copy of the gene in the patient (*How does gene therapy work?: MedlinePlus Genetics*, 2021). How is the normal copy of the gene introduced? Vectors are genetically engineered carriers that deliver genetic material in the form of plasmids or viruses. Viruses are the preferred carrier because they are efficient at invading cells and inserting their genetic material (Gonçalves & Paiva, 2017). This may seem counterintuitive because of the

nature of a virus, but these viruses are modified using recombinant (genetic material formed by recombination) DNA technology so that they do not cause diseases among their host patients (Wirth et al., 2013). In order to be able to treat a specific section of cells, understanding genetics in depth as well as the disease of interest is crucial. The vector that is releasing the gene is chosen selectively because it must fit several criteria. Vectors should:

“Display efficiency in the release of one or more genes of the sizes necessary for clinical applications, not be recognized by the immune system, and be purified in large quantities and high concentrations so that it can be produced and made available on a large scale” (Gonçalves & Paiva, 2017).

There are additional criteria for vectors, and it is evident that the process of gene therapy is complex in part due to the carefulness that must be exhibited in the method of inserting new genetic material. When we take into consideration neurodegenerative diseases such as Parkinson's, Huntington's, or Alzheimer's Disease, the complexity is heightened by the precautions that come with utilizing neurosurgical techniques. The reason why current treatments for these diseases aim to relieve symptomatic symptoms instead of the underlying pathology is because it is a simpler solution. However, pharmacological medications can only provide relief of symptoms to an extent. Due to the selectivity of the blood-brain barrier, which is a function of the brain that prevents certain molecules from entering it while allowing others to enter, higher doses of treatment cannot be given to patients because they increase the risk of invoking toxicity and damage (Sudhakar & Richardson, 2018). Furthermore, the effectiveness of pharmacological treatments is reduced as the illness progresses, which makes patients more susceptible to harmful side effects. Gene therapy is an alternative solution that works around these obstacles in disease

treatment by focusing on a specific anatomical area to avoid unnecessary interactions with other brain regions.

Modified viral vectors are the key method of delivery for genes to the brain, but adeno-associated viruses in particular have been used in clinical trials for central nervous system (CNS) disorders. Adeno-associated virus vectors (AAVs) are safe and helpful for *in vivo* (within an organism) as opposed to *ex vivo* (outside of an organism) gene therapy, and it bodes well for monogenic (controlled by one gene) disorders with post-mitotic problems (Kaufmann et al., 2013). *In vivo* gene therapy involves introducing the new genetic material directly into the body through a muscle or other area while *ex vivo* gene therapy involves changing a patient's isolated cells and reintroducing them into their body. Adeno-associated viruses work by introducing DNA into the nucleus of a cell without having it become a part of a chromosome. They can conduct gene transfers to both mitotic and postmitotic cells, they show no cytotoxicity (being toxic to cells), and they can maintain stable transgene expression in the brain for over 10 years (Choudhury et al., 2017). Perhaps more importantly, adeno-associated viruses are able to breach the blood-brain barrier once they are injected through either an intrathecal (spinal), intraventricular (ventricle of the brain or heart), or intravascular (vessel) path to the brain. Alternatively, if the genetic material is combined with a chromosome, then this type of viral vector is known as a retrovirus. Retroviral vectors are generally preferred for gene transfer into proliferating, or multiplying, cells because of their ability to integrate with a host chromosome (Kaufmann et al., 2013).

It is adeno-associated viral vectors that hold potential for treating neurodegenerative diseases, including Parkinson's Disease. Many people are aware that Parkinson's Disease is associated with a loss of dopaminergic neurons in a brain region called the substantia nigra. They

may know that dopamine, as well as another neurotransmitter called GABA, are involved in the disorder. Dopamine is known to assist in controlling movement while GABA is an inhibitory neurotransmitter, meaning it helps to prevent or reduce certain behavioral and cognitive responses. Since Parkinson's Disease deals with motor function problems, it is essential that both of these neurotransmitters function properly. However, they may not know about the two treatment methods that have been used in adeno-associated gene therapy clinical trials. There are two particular strategies that have been tested: the first involves gene transfer of a protein called glutamic acid decarboxylase (GAD) as well as a protein called aromatic l-amino acid decarboxylase (AADC). GAD allows for the production of the neurotransmitter GABA, while AADC produces dopamine. The second strategy attempts to restore cellular functions that are affected by Parkinson's Disease through *in vivo* gene transfer of a neurotrophic (relating to nervous tissue growth) protein called glial derived neurotrophic factor (GDNF).

The results were promising, albeit not revolutionary as there is still much research to be done. The GAD method was aiming to deliver GAD through the subthalamic nucleus (STN) in order to increase GABA inhibition. This actually reduced motor symptoms of Parkinson's Disease and the subjects had an overall improvement in their Unified Parkinson's Disease Rating Scale (UPDRS) scores (Sudhakar & Richardson, 2018). The AADC treatment showed improved motor functions in non-human primates and improvements in the UPDRS among human patients. On the other hand, GDNF showed the most promise at improving Parkinson's Disease pathology, specifically in animal subjects. Gene therapy with AAV ended up improving clinical rating scores and even increased dopamine production. Multiple animal studies have shown that AAV-GDNF injections into the putamen (component of the basal ganglia) is both safe and effective at treating Parkinson's Disease behavioral symptoms (Axelsen & Woldbye, 2018). Due

to these results, there is now an NIH funded, FDA approved phase 1 trial that is delivering several different doses of these viral vectors in patients with severe Parkinson's Disease (Sudhakar & Richardson, 2018).

With this being said, there have also been plenty of clinical trials utilizing other methods that have had modest results. Even with trials where phase one shows success, oftentimes phase two does not produce significant improvements that have longevity. Interventions to change firing patterns or increase dopamine levels in the brain have less effectiveness as dopaminergic neurons continue to degenerate (Choudhury et al., 2017). Neurodegenerative diseases are complicated, and when the pathology isn't understood in its full depth this makes it harder to effectively use gene therapy, which is a relatively new solution in itself. However, this doesn't mean that gene therapy should be given up entirely. The fact that there has been success at all in increasing dopamine turnover or reducing motor symptoms shows that research is heading in the right direction. As more clinical trials are conducted, new insights are revealed about the role that gene therapy can play in treating Parkinson's Disease as well as other neurodegenerative disorders.

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