

2024 NJABR High School Essay Contest
2nd Place

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For as long as I can remember, my grandmother has been battling Parkinson's disease (PD). Over time, the dopaminergic neurons in a region of her brain called the substantia nigra have died, meaning her brain can't properly signal voluntary movements. As a result, I've watched my grandmother slow down, her hands and legs shaking more and more as her brain continues to lose dopamine. Her tremors cause her legs to give out, leading her to suffer dangerous falls each year. She's gone from spoon-feeding me as a child to becoming nearly bedridden because she could easily hurt herself if she gets up. Since the origins of PD remain unknown, there is no cure for her condition. Instead, she has to take a slew of pills to control her symptoms.

Ever since I learned about neuroscience and biomedical research, I've wanted to explore how my grandmother's treatments work. I found that the chief medication she takes contains levodopa (L-dopa), a precursor to dopamine developed in the 1960s. When ingested, L-dopa slips past the blood-brain barrier, enters the brain, and is converted by L-amino acid decarboxylase (AADC) into dopamine, restoring dopamine levels and activating more neurons to better contract muscles, mitigating slowness and tremors. There is, however, a significant side effect of long-term L-dopa treatment: levodopa-induced dyskinesia (LID), or the development of involuntary jerky movements after treatment. The exact cause for this is unknown, but it may have to do with how neurons respond to dopamine immediately after treatment and as the treatment wears off. Regardless of its causes, LID can severely disrupt a patient's daily activities, so new treatments are being developed to lower a patient's reliance on L-dopa.

Dopaminergic neurons are, by definition, rich with dopamine, so it follows that they would also be rich with the protein needed to produce that dopamine - AADC. Therefore, it is suspected that PD progression is devastating not only because dopamine levels diminish, but also because the AADC needed to replenish it dwindles simultaneously. This means that as PD progresses, patients need to increase their dosages to relieve the same symptoms. Instead of increasing dosages to no avail, why not teach the body how to make more AADC? In a nutshell, this is what AAV2-hAADC gene therapy achieves: a harmless adeno-associated virus (AAV2) transfers some DNA into neurons, which can read it and synthesize functional human AADC (hAADC), allowing for quicker dopamine production. A phase 1 clinical trial published in 2022 tested this method on 17 patients with moderately advanced PD. After three years, researchers found that the patients had increased AADC activity, scored lower on the UPDRS III scale (a way to measure the severity of PD symptoms), had minimal dyskinesia progression, and lowered their medication requirements by 21 to 30%. Gene therapy had clearly made the patients more

responsive to standard treatment and mitigated the effects of LID. While AAV2-hAADC therapy as a complete PD treatment remains in the early stages of research, this study demonstrates that this option has great potential and should be investigated further.

Animal testing has always been important in biomedical research, but it has certainly been critical for neuroscience given the risks that come with experimental treatments. In fact, the study detailed above relied on an eight-year-long experiment on monkeys. The researchers in that study began by lesioning the brains of eight monkeys with MPTP, a chemical known to mimic the effects of PD. Then, they injected four monkeys with AAV2-hAADC and four with AAV2-LacZ (a virus carrying a nontherapeutic gene). They then ran PET scans at varying intervals to track AADC expression and found that it was restored in the area where they gave the treatment and remained stable for eight years. This indicates that gene therapy can be a long-term solution for ameliorating PD systems. Without the promising results of this study, gene therapy could not have been tested on humans.

For the time being, Parkinson's disease will continue to affect millions like my grandmother. However, decades of research and biomedical breakthroughs - such as the tried-and-true L-dopa and now gene therapy - have brought us closer and closer to a real cure for PD. If a cure is to be developed within the next decades, we must continue to fund biomedical research. We also can't forget the outstanding contributions animals have made, as all biomedical breakthroughs begin with animal testing. With L-dopa treatment, my grandmother has remained incredibly resilient against her Parkinson's, and for that, I thank the efforts of biomedical researchers around the world.

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