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Gene Therapy for Parkinson's Disease: Still a Hot Topic?

Parkinson's disease is a synucleinopathy with widespread degeneration within the peripheral nervous system and across a variety of brains regions. The best studied and understood region of neural degeneration is the dopaminergic nigrostriatal system. Striatal dopamine insufficiency and nigral neuronal loss underlie the cardinal motor symptoms of PD. Levodopa and deep brain stimulation (DBS) are the most potent therapies for these symptoms. However, they have side effects that warrant the investigation of new therapies.

One novel therapy is gene transfer (or therapy), in which, for the most part, viruses are used to deliver therapeutic molecules. Gene therapy methodologies can be divided into two general types: symptomatic and disease modifying (for review, see Kordower and Bjorklund, 2013). The first gene therapy clinical trial for PD was the delivery of aromatic amino decarboxylase (AADC) (Mittermeyer *et al*, 2012). This approach was aimed at symptomatic benefit. AADC is the enzyme that converts levodopa to dopamine and AADC gene delivery attempts to make the conversion of the exogenous levodopa to dopamine more efficient. In animal studies, lower doses of levodopa result in the same antiparkinsonian benefit as high doses when it is combined with gene delivery of AADC. Lower doses would also obviate or delay the emergence of dopa-induced dyskinesias. AADC gene delivery was safe and well tolerated in a Phase 1 clinical trial (Mittermeyer *et al*, 2012). An open-label assessment demonstrated some benefit in a small number of patients. Oxford Biomedica employed a equine lentivirus to deliver tyrosine hydroxylase, AADC, and GTP cyclohydrolase, the combination of which makes dopamine. Preclinical studies in rodents and monkeys delivering lenti-dopamine demonstrated significant antiparkinsonian benefit. A Phase 1/2 clinical trial has been completed again demonstrating safety and tolerability with some measure of efficacy as determined via open-label assessments (Palfi *et al*, 2014). Another series of studies models gene therapy after deep brain stimulation (DBS). In PD, the subthalamic nucleus is hyperactive and DBS blocks that hyperactivity. Glutamic acid decarboxylase (GAD) reduces cellular activity and reverses motor dysfunction in rodent and nonhuman primate models of PD. A Phase 2 randomized sham controlled trial was performed and met the primary endpoint (LeWitt *et al*, 2011). However, the magnitude of the effect was small and it is unclear whether this approach is going forward.

Disease-modifying gene therapy strategies have focused on the glial cell family of ligands (GFLs), namely, GDNF and neurturin. Gene delivery of both of these trophic factors protects nigrostriatal circuitry and motor function in numerous rodent and nonhuman primate models of PD (Kordower and Bjorklund, 2013). A new clinical trial using gene delivery of GDNF is currently underway. Unfortunately, two Phase 2 clinical trials testing neurturin failed (Marks *et al*, 2010; Olanow *et al*, manuscript in preparation). Why is this molecule so potent in preclinical models but ineffective in patients with PD? We have postulated that the failure is due to the extensive degeneration of the nigrostriatal system at the time the patients were treated (Kordower *et al*, 2013). Furthermore, the few fibers that are remaining are defective in axonal transport mechanisms and thus the trophic factor fails to be efficiently transported, either retrogradely or anterogradely, to nigral perikary.

Gene therapy for PD still has great promise. Multiple approaches are safe and well tolerated. However, at this time, no study has demonstrated *robust* clinical benefit using rigorous double-blind assessments. However, it is possible that a resolution of delivery issues, which will maximize the spread of the vector to the target area, as well as moving to a less-impaired patient population, might unlock the potential of this strategy. Additionally, as currently practiced, gene therapy for PD only addressed the cardinal motor symptoms, and other signs, including potentially disabling psychiatric symptoms, require a different gene therapy approach.

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