

What's Hot in Parkinson's Disease

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Michael S. Okun, M.D., National Medical Director

Update on Gene Therapy for Parkinson's Disease

A common question asked by many patients and families afflicted with Parkinson's disease is, "what is gene therapy?" Quite simply, gene therapy is placing genetic information (DNA) into the cells and tissues of humans with Parkinson's disease. In the purest form a defective part of the genome is replaced with a new copy. Perhaps the most interesting part of the evolving story of gene therapy has been the use of a virus as a vector to carry the genetic information into the brain. These viruses have been deactivated and can be safely used for this purpose^{14, 15}.

There are three large ongoing gene trials in humans with Parkinson's disease. The first aims to deliver amino acid decarboxylase (Company sponsoring is Avigen) which is a brain enzyme that may help enhance the effectiveness of dopaminergic medicines like levodopa (Sinemet), and perhaps reduce the doses drugs, and consequently their side effects. The second trial delivers neurturin which is a protein that may repair and rescue dopamine cells in the brain. Neurturin¹⁶⁻¹⁸ (Company sponsoring- Ceregene). Neurturin belongs to the same protein family as glial cell derived neurotrophic factor (GDNF), which was another gene therapy which had disappointing results in a recently publicized trial (Company sponsoring- Amgen)¹⁶⁻¹⁸. The final trial focuses on an enzyme called glutamic acid decarboxylase (GAD) (Company sponsoring- Neurologix)^{14, 17, 19-21}.

Kaplitt and colleagues reported in Lancet in 2007, the "Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial."^{22, 23} The subthalamic nucleus (STN) is a brain structure that spews a chemical called glutamate onto another structure in the brain called the globus pallidus. Many treatment schemes have focused on controlling or neuromodulating the output from the STN. One such approach has been inserting a lead into the brain and introducing electricity in order to change the firing pattern and rate emanating from the STN (deep brain stimulation). Kaplitt and colleagues have developed the innovative approach of using gene therapy to change the STN from a chemically excitatory nucleus to a chemically inhibitory one. These investigators measured the safety, tolerability, and preliminary efficacy of the "transfer of glutamic acid decarboxylase (GAD) gene with adeno-associated virus (AAV) into the STN of patients with Parkinson's disease." The original study published in Lancet had 11 patients. The group was similar to those used for deep brain stimulation (less than 70 with on-off motor fluctuations and minimal cognitive dysfunction). The most important outcome was "no adverse events related to the gene therapy. Significant improvements in

motor UPDRS motor scores ($p=0.0015$), predominantly on the side of the body that was contralateral to surgery, were seen 3 months after gene therapy and persisted up to 12 months.^{22, 23}

The relative magnitude of the changes in the UPDRS seemed to be roughly similar to what has been observed following deep brain stimulation, although longer term follow-up of motor symptoms will be needed. Many experts have held that gene therapy has a high “bar” to pass, as the results of deep brain stimulation have provided excellent benefits in a similar group of patients. Preliminary analyses point to the benefit (similar to deep brain stimulation) as being predominantly in motor function and not in areas of non-motor or levodopa resistant symptoms (depression, sleep, gait, communication, etc.). No one knows if changing the excitatory function of the nucleus into inhibitory will affect learning, but this is a point that will require close follow-up²⁴. Perhaps the most important finding was that gene therapy was successfully used in humans with Parkinson's disease, and that this success may open the door to future gene therapies, as well as to combination therapies (genes plus stem cells or genes plus medications, or genes plus deep brain stimulation).

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