Promises and Pitfalls of Gene Therapy in Parkinson's Disease

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Gene therapy was heralded as a potential cure for Parkinson's disease (PD) beginning in the 1990s. The idea was that by giving patients the genes they need, potentially their functionality could be restored. However, several initial clinical trials failed to provide positive results. These failures have provided lessons for the development of alternative potential gene therapies as well as other approaches, such as augmenting pharmacotherapy with gene therapy. Several new agents and techniques are currently in early-stage clinical trials. Dawn E. Bowles, PhD, Duke University, Durham, North Carolina, USA, described the basic principles of gene therapy using heart failure as an example.

There are 4 main requirements for gene therapy to be successful: the molecular target must be appropriate for the disease state of interest, there must be an appropriate model for the disease, successful vector design is needed, and methods of targeting the vector to a tissue or specific cells of interest are needed.

A biobank is a repository that collects and stores biologic samples, and biobanks are evolving into information banks that will supply data from validated medical records, molecular data, and patient demographics. As such, biobanking represents an important source of data for biomarkers and gene therapy.

Most vectors that have been used in clinical trials of gene therapy are viral vectors. In particular, Dr. Bowles focused on adeno-associated virus (AAV), a member of the parvovirus family. AAV is a very small virus that requires a helper virus to enable it to infect its host. It is not known to cause pathology. Concepts that must be considered include viral genes present on the vector, the pathogenicity of the virus, the immunogenicity of the virus, and persistence. All of these characteristics may be maintained or removed, depending on the downstream application of the vector. Recombinant AAVs are produced by removing the replication and capsid genes and replacing them with a transgene of interest. The discovery of additional serotypes of AAV led to the ability to use rational design for vectors; different serotypes transduce different targets more efficiently than others. In addition, the successful crystallization of AAV provided a greater understanding of the function of different amino acids in the viral structure.

Jeffrey Kordower, PhD, Rush University Medical Center, Chicago, Illinois, USA, discussed the use of gene therapy to deliver trophic factors as an intervention for PD and why recent clinical trials for this application have failed. Multiple characteristics of glial cell–derived neurotrophic factor (GDNF) suggested that it may be a promising target for PD, including the promotion of midbrain dopaminergic neurons and the prevention of degeneration in multiple animal models. However, GDNF unfortunately did not enhance nigrostriatal function in patients with PD, because the region the trophic factors were targeting did not contain dopaminergic fibers.

Dr. Kordower stated that patients who would benefit from deep-brain stimulation are the same population that would benefit from gene therapy. He noted that the purpose of gene therapy is not to save nigral neurons but to enhance striatal dopaminergic innervation.

Some underlying reasons for gene therapy failure begin in the preclinical stage. For example, a majority of research is performed in young animal models, yet many diseases, including PD, are a phenomenon of aging. Therefore, it makes sense that work in the future should be performed using aged animals. In addition, positive results in animal models often do not translate to humans. For example, in a study, one might induce PD in an animal and then administer treatment 1 week later. Dr. Kordower pointed out that the striatum in this animal is not accurately modeling the striatum of a human patient with PD, as this is not the normal course of events.

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Dr. Kordower's research on GDNF could not continue, because he was unable to obtain the license to the GDNF gene. As a result, he began to study neurturin, which produces similar *in vitro* effects as GDNF. Following positive results of neurturin in monkey models of PD, neurturin was found to be well tolerated in an open-label, Phase 1 trial in humans. Efficacy between 12 and 18 months appeared to favor the neurturin arm of the trial, but ultimately, neurturin failed to demonstrate efficacy as a treatment for PD. Why was neurturin ineffective? Dr. Kordower highlighted that there is not a large concentration of neurturin in the human brain. In addition, in an area with a large amount of neurturin, there is little evidence of upregulation of tyrosine hydroxylase (TH) at 3 months after neurturin injection. Furthermore, unlike in the monkey models, after 5 years of disease duration, there were no fibers left in the striatum to transport neurturin from the striatum to the nigra to exert its effects. Finally, although GDNF, and therefore neurturin, can protect neurons from a variety of insults, they do not protect neurons from synucleinopathies, and PD is a synucleinopathy. Therefore, when evaluating a novel agent for the treatment of PD, it is important to consider and understand what remains anatomically as the disease progresses and what structural and functional changes may occur.

Tomas Björklund, MSc, PhD, Lund University, Lund, Sweden, discussed augmenting dopamine delivery with gene therapy for the treatment of PD. One function of dopamine is to facilitate movement in a more fluid manner than other neurotransmitters. If there is a loss of dopamine synapses, there are often some dopamine fibers still remaining. The purpose of augmenting dopamine delivery is to use gene therapy to replace enzymes important in symptom control, not to stop disease progress. The aromatic amino acid decarboxylase (AADC) enzyme is important for conversion of levodopa (L-dopa) to dopamine. Dopamine cannot cross the blood-brain barrier, whereas L-dopa can. Therefore, central AADC activity is critical for L-dopa therapy to be successful.

There are 3 types of gene therapy for enzyme replacement in PD. The first is to facilitate pharmacotherapy with L-dopa for PD, so that L-dopa can reach sites of the brain where it is needed most. This is achieved by replacing AADC. In addition to symptom control, this is advantageous in that it theoretically could allow dose reduction, which would decrease the occurrence of adverse events, such as dyskinesia. Recombinant AAV–AADC gene therapy was found to be safe in two Phase 1 trials [Muramatsu S et al. *Mol Ther* 2010; Christine CW et al. *Neurology* 2009].

The second type is 2-gene enzyme replacement, also referred to as a continuous dopa delivery strategy [Nyholm D. *Parkinsonism Relat Disord* 2007; Olanow CW et al. *Lancet Neurol* 2006], whereby TH and guanosine triphosphate cyclohydrolase (GCH1) are introduced with gene therapy to replace dopamine production in the brain. With disease progression, the therapeutic window of oral intermittent L-dopa pharmacotherapy is decreased, and after 12 years of disease duration, it may even be gone. Viral vector–mediated continuous dopa delivery may in this scenario provide a route to bring back the therapeutic window without the emergence of dyskinesias.

The third type is one in which all 3 enzymes involved in dopamine production (TH, GCH1, and AADC) are replaced, which would essentially replace dopamine in the brain. However, all 3 genes cannot fit within AAV; therefore, the lentivirus equine infectious anemia virus (EIAV) was used. An open-label, Phase 1/2, dose escalation trial used the dopamine replacement approach with the EIAV vector in patients with PD [Palfi S et al. *Lancet* 2014]. Patients experienced an improvement of about 12 points on the Unified Parkinson's Disease Rating Scale, without severe adverse events at 12 or 24 months.

Several approaches of gene therapy are currently being investigated for the treatment of PD. Although gene therapy with neurturin failed, its development and testing provided lessons that can be used for the development of other gene therapies. Noncurative gene therapy approaches, such as augmenting or replacing dopamine in the brain, are currently in early-stage clinical testing.