Gene therapy for Parkinson's disease: current approaches and future directions

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'...future therapies could be directed towards inactivating genes that have been identified in familial PD such as the parkin, *LRKK2* and *PINK1* gene mutations.'

Advances in the field of gene transfer technology have led to interventions that utilize the expression of exogenous genes to treat disease. Exogenous genes can be introduced into a patient in two ways, utilizing an *in vivo* or an *ex vivo* approach. *In vivo* gene therapy is a process whereby a gene is inserted directly into the cells of a patient utilizing a vector. *Ex vivo* gene therapy involves the genetic manipulation of cells or tissue outside the patient, and then employing this genetically modified tissue as a therapeutic agent. Gene therapy holds great promise for the treatment of neurodegenerative disorders, although several important issues still need to be addressed. These include:

- Better understanding of the role of specific genes and their protein products in the symptom manifestation and pathogenesis of disease
- Insuring the safety of genetic vectors and the genes expressed
- Improving means for overcoming the BBB without increasing the risk of immune response

As knowledge regarding these important issues has expanded, several promising gene therapy initiatives have been undertaken to treat Parkinson's disease (PD), and it is likely that new gene therapy approaches for PD and other neurodegenerative disorders will follow.

Currently, three gene therapy approaches to PD are being examined in clinical trials. Results of the first gene therapy trial in PD have recently been published [1]. In this study, the investigators examined the safety and efficacy of subthalamic nucleus (STN) infusion of an adenoassociated virus vector containing the gene for glutamic acid decarboxylase (AAV-GAD). The rationale for

this approach is that in PD, the STN is overactive (disinhibited) because of decreased GABAergic input from the external pallidum. This results in increased release of the excitatory neurotransmitter glutamate into the internal pallidum and substantia nigra reticulata. The introduction of the GAD gene into the STN should catalyze an increase in local GABA, thereby inhibiting STN firing. The study found the procedure to be safe and well tolerated in 12 subjects followed for 1 year. In addition, imaging and clinical assessments suggested an improvement in parkinsonism, although this will need to be confirmed in future double-blind, placebo-controlled trials.

Another promising gene therapy approach to treating PD currently in human clinical trials involves the introduction of the gene for aromatic L-amino acid decarboxylase (AADC) into the striatum [2,3]. The rationale for this approach is that advanced PD is characterized by increasing loss of nigrostriatal neurons resulting in reduced striatal AADC activity and decreased efficiency of levodopa conversion to dopamine. By increasing AADC activity in the striatum through gene therapy, it is hoped that treatment with levodopa will have a prolonged and more potent effect. Initial reports suggest this approach is safe, although a formal report of the results has not yet been published.

'Gene therapy holds great promise for the treatment of neurodegenerative disorders.'

Gene transfer therapy approaches to neuroprotection and neurorestoration are also being developed for PD. Neurturin, a glial-derived neurotrophic factor family member, delivered via an AAV vector, has been studied in a Phase I trial involving 12 PD subjects. Although the results from this trial have not formally been published, earlier animal studies provided promising results [4,5]. Initial reports from the Phase I study presented in abstract form suggest that the therapy is generally safe, and preliminary clinical and fluorodopa (F-DOPA) PET imaging efficacy results in this open-label,

uncontrolled trial appear promising. The therapy has now entered a Phase II double-blind, controlled clinical trial.

There are many potential gene therapy targets for PD. For example, future therapies could be directed towards inactivating genes that have been identified in familial PD, such as the parkin, *LRKK2* and *PINK1* gene mutations. Another approach might be to build on current strategies. For example, gene therapy to augment the activity of several enzymes including AADC, tyrosine hydroxylase and GTP cyclohydrolase I may be more efficacious than one enzyme alone, and such an approach has shown promise in early animal models [6,7]. As new genetic risk factors for PD are discovered, and knowledge regarding the pathophysiology of PD advances, new gene-therapy targets for PD are likely to emerge.

‘Several gene therapies for PD are already in clinical trials and appear to be safe and well tolerated.’

As with all novel therapies, safety issues are paramount in gene-therapy trials. This is especially true in PD, a disease for which effective traditional therapies already exist. Although no major safety concerns have so far arisen in the three gene-therapy trials described above, only a relatively small number of patients have been treated, and the follow-up period has been relatively brief. Future clinical trials will need to be undertaken with great care, both in patient selection and long-term follow-up. A recent death in a gene-therapy trial utilizing an AAV vector in patients with arthritis [101] highlights the need for continued vigilance regarding safety monitoring in gene-therapy trials. In broad terms, the risks of gene therapy can involve the viral vector itself or the effects of the gene being introduced. In both cases, unforeseen adverse events can occur. Although AAV so far appears to be safe as a vector in PD clinical trials, relatively few patients have received gene therapy, so ongoing and future clinical trials will need to monitor safety extremely closely. With regard to the risk of specific genes, unforeseen adverse events remain a concern. To address this, gene-regulation systems are being developed. These systems, utilizing promoters that are sensitive to externally administered drugs such as tetracycline, RU486 and rapamycin [8,9], could offer the ability to modulate gene expression

should a serious adverse event occur. At the current time, none of these methods are ready for human clinical trials. Given the potential of gene therapy for treating devastating neurodegenerative disorders, it is likely that gene-therapy clinical trials will continue without these gene-regulation systems, however they will likely be incorporated in the future.

‘...new approaches, combined with new technologies for delivering and modulating the expression of genes, offer great hope for major advances in the treatment of PD and other neurodegenerative disorders.’

Gene therapy for PD and other neurological disorders currently requires neurosurgical intervention, which carries the potential for surgical and anesthetic complications. Methods for circumventing the BBB with peripherally administered vectors have not yet been clinically introduced. However, several technologies using peripherally administered vectors are being investigated and hold promise. Liposomes are synthetic lipid membrane-bound vesicles that have the capacity to carry genetic information. When coated with polyethylene-glycol (PEG), liposomes become stable in the blood, and further modification with an antigen that allows for active transportation across the BBB produces a pegylated immunoliposome (PIL) [10,11]. In animal models of PD, peripherally administered PILs have been successfully utilized for gene therapy. For example, in 6-hydroxydopamine-treated parkinsonian rats, PILs containing the gene for tyrosine hydroxylase (TH) successfully restored TH activity in the brain [12]. This strategy for delivering genetic material to the CNS holds promise for future gene-therapy approaches for PD and other neurodegenerative disorders. Nonetheless, some gene therapy strategies, such as the STN AAV-GAD approach described above, require regional brain targeting of gene therapy, and it is unlikely that this will be achievable with peripherally administered therapies.

Gene therapy represents an exciting new approach to the treatment of PD and other neurodegenerative disorders. Several gene therapies for PD are already in clinical trials and appear to be safe and well tolerated, although relatively few PD patients have been studied. Future randomized, double-blind trials in larger cohorts will be needed to fully assess the

safety and efficacy of these novel therapies. As the genetic risk factors and the pathophysiology of PD are further elucidated, new gene therapy approaches are likely to emerge. These new approaches, combined with new technologies for delivering and modulating the expression of genes, offer great hope for major advances in the treatment of PD and other neurodegenerative disorders.

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Website

- US FDA statement on Gene Therapy Clinical Trial
www.fda.gov/bbs/topics/NEWS/2007/NEW01672.html

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