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Gene therapy for Parkinson's disease

Parkinson's disease is characterized by loss of dopaminergic neurons in the substantia nigra. The loss of these neurons results in a change in the balance of excitatory and inhibitory pathways in the brain, and these pathways in turn affect movement control. Medication therapies, and in particular dopamine replacement therapies were developed in the late 1960s and remain the mainstay of therapy. More recently, surgical treatments (pallidotomy or deep brain stimulation of selected targets in the brain) have been developed to improve motor function by normalizing increased brain cell activity due the loss of dopamine releasing cells which occurs as a consequence of reduced dopamine release.

People with Parkinson's disease generally respond well to medication for a number of years. However with long-term treatment, the response to medication—especially to levodopa—may fluctuate. The most common “motor fluctuation” is called **wearing off**. Wearing off may develop years after beginning treatment with a dopamine agonist or levodopa. It occurs when the benefits of the prior dose are beginning to wane and is often appreciated as recurrence of tremor or slowness in the hour before the next dose of medication is taken. The other main motor fluctuation is involuntary twisting turning movements called **dyskinesias** which typically occur in the hour or so after taking dopaminergic therapies. Medications (*insert link*) and deep brain stimulation (*insert link*) are described in other modules. In this module, the potential advantages of gene therapy will be discussed.

Gene therapy has a number of potential advantages that may be useful in progressive medical conditions. Conceptually, it is a means of making cells produce a protein that they normally do not produce that might improve a particular condition. The technique inserts genes that provide specific genetic instructions that cells use to produce a desired protein. The treatments produce proteins that are involved in normal cellular processes and may therefore be less likely to cause side effects. Moreover, gene therapy can be targeted to a specific location where the treatment is needed, which also may limit possible side effects. Finally, gene therapy does not rely on the placement of devices that may fail due to mechanical or electrical reasons. A number of proteins have already been used for gene therapy for Parkinson's disease. The choice depends on the **treatment strategy**. For example one strategy is to improve the delivery of dopamine to the relevant brain regions in Parkinson's disease. Other strategies have tried to provide growth factor support to brain regions with the expectation that this might help damaged nerve cells to recover and thus slow Parkinson's disease progression or reverse it.

Gene therapy relies on transporting small pieces of genetic material, or DNA, into the targeted brain cells. Because human bodies have developed a number of enzymes that breakdown unprotected DNA, most gene therapies use some sort of “protective envelop”, called a **vector**, to carry the genetic material and deliver the gene to targeted cells. The most common vectors include adeno-associated virus type 2, lentivirus, adenovirus, and herpes simplex virus. Only viruses that have lost their ability to reproduce themselves and do not cause disease are selected as vectors for gene therapy. Adeno-associated virus type 2 (AAV-2) has particular advantages. It carries genetic material only to neurons (not to the other supporting cells of the brain) and once within the brain it is particularly efficient in carrying the genetic material to the neurons affected in Parkinson's disease. Most gene therapy studies in Parkinson's disease have used AAV-2 as the vector. Lentiviruses have also been studied extensively. Because of their larger capacity, lentivirus is the vector when more than one gene is used.

Once a gene and vector have been selected, the treatment must be administered to the relevant area of the brain. The studies performed thus far have been directed to particular regions of the **basal ganglia**. The basal ganglia are number of interconnected deep brain regions that are involved in movement control. A major pathway connects the **substantia nigra** to the **putamen** (where dopamine is normally released) and then to the **globus pallidus** directly or by way of the **subthalamic nucleus**. To date, gene therapy for Parkinson's disease has been administered by drilling a hole in each side of the skull and then injecting the selected dose of the viral vector (containing the gene) into the desired brain region (either putamen or subthalamic nucleus) using image-guided surgical techniques. These treatments are performed either in a standard operating room or in a specialized radiology suite. Recovery from these procedures is usually quite rapid, with most patients being discharged home 1 or 2 days after gene therapy.

In the descriptions below, reference will be made to the clinical studies conducted thus far in humans. **Phase 1** studies refer to small studies, usually 10-15 patients at a single institution. These studies are designed to determine the safety and possible benefit of a particular treatment and no untreated comparison group is recruited. If a phase 1 study shows that a treatment is well tolerated and provides some evidence of benefit, a phase 2 study may be performed. **Phase 2 studies** are larger (typically 30-60 patients), are conducted at a number of medical institutions, and a control or placebo group is included for comparison to the group treated with the gene therapy. Humans in research studies often obtain substantial improvements that are unrelated to the specific treatment they receive. The improvement may be due to the expectation of benefit from treatment. This phenomenon is called the **placebo effect** and can be quite substantial in patients with Parkinson's disease. Therefore using a “control” or untreated group is considered crucial in determining whether a treatment offers true benefit, beyond the placebo effect. Because gene therapy involves surgical treatment, a simulated or “**sham**” surgical procedure is necessary in gene therapy studies. These sham surgical procedures usually involve drilling small holes in the skull but not injecting the brain with the gene therapy under study. In the studies, investigators who perform subsequent evaluations of the patients are also unaware of whether the patient underwent the gene therapy or the sham procedure. This is called a **double-blind** study since neither the subject nor the investigator who performs the routine

visits knows the treatment status of the patient. Double-blind studies are considered fundamental in determining whether a treatment offers a true benefit. If a study treatment shows safety and benefit in a Phase 2 study, a **Phase 3** study may then be performed. This study is similar to a Phase 2 study but is larger study (usually involving hundreds of patients) and is designed to confirm the treatment effectiveness, monitor side effects, and collect information that will allow the treatment to be used safely. Information from a successful Phase 3 studies (along with other information about the study treatment) is then used by the United States Food and Drug Administration (FDA) to determine whether a new treatment is approved for routine treatment of a medical disorder.

Regarding therapeutic strategies, 3 approaches have been developed thus far. These are as follows:

- (1) The first approach is to **increase dopamine production** in specific regions of the brain. One study using this approach approaches uses the gene for the enzyme **aromatic amino acid decarboxylase (AADC)**. This enzyme converts levodopa into dopamine, a neurotransmitter that is deficient in Parkinson's disease. Studies have shown that AADC is gradually lost in Parkinson's disease. The progressive loss of this enzyme is thought to contribute to the need to increase levodopa doses as time goes on. The rationale for this approach is that if a greater amount of AADC is present in the location where dopamine should be released, then a more reliable and perhaps a more robust response to levodopa will occur. Moreover, it is possible that a patient who no longer is obtaining a reliable benefit from levodopa therapy might regain responsiveness to this treatment after gene therapy with AADC. Inherent in this approach treatment is that the patient may alter the effect of his gene therapy by adjusting his daily dose of levodopa, since the effect of this therapy depends on continuing treatment with levodopa. A phase 1 study in which AADC was injected into the putamen has been completed at 2 different doses. In the 10 patients treated, clinical rating scales and diaries of motor function suggested benefit and specific imaging studies provided evidence of successful gene therapy.
A variation on this strategy uses 3 genes that produce the enzymes AADC, tyrosine hydroxylase (TH), and GTP-cyclohydrolase-1 (GCH-1). Together these 3 enzymes can generate dopamine independent of external levodopa. The advantage of this approach is that it may be possible for the patient to discontinue treatment with levodopa. Although this approach seems very attractive, there are concerns that its benefits relies on producing precisely the right amount of dopamine. For example, too high a dose of gene therapy might result in complications due to excessive production of dopamine. The results of the study should be published in the near future.
- (2) The second gene therapy strategy is to **adjust or modulate the excitatory and inhibitory pathways** of the brain. The rationale of this approach is that the nerve cells of the subthalamic nucleus are overactive and that release of an inhibitory neurotransmitter in this brain region might normalize these cells. The gene for the enzyme **glutamic acid decarboxylase (GAD)**, which produces the inhibitory

neurotransmitter called GABA, has been examined in a phase 2 study in which 45 subjects were randomized to either bilateral treatment with GAD or a sham or simulated surgical procedure. While both patient groups showed improvement at 6 months, the improvement was greater in the subjects who underwent GAD treatment. Overall this study provided support for both the efficacy and safety of this approach.

(3) The third approach is using brain proteins, termed **growth factors** (because of their role in brain development), that might protect against progression of Parkinson's disease or possibly even reverse it by stimulating regrowth of injured nerve cells. A number of growth factors have been identified over the years. These include glial cell line-derived neurotrophic factor (GDNF) and Neurturin which is similar to GDNF and shares the ability to promote the survival of dopaminergic neurons. In models of Parkinson's disease, GDNF and Neurturin have been shown to promote the survival of dopaminergic neurons. Both a phase 1 and phase 2 study using Neurturin gene therapy targeted to the putamen have been performed. In the phase 2 study, 38 patients were randomized to Neurturin gene therapy or to sham surgery. Unfortunately, there was no significant difference in the main outcome measures at 12 months. While the lack of benefit in the main outcome measures was disappointing, a subgroup of patients followed for 18 months was slightly better in the Neurturin patient than the sham treatment group, suggesting that slightly longer period of observations might be necessary to see a benefit with this gene therapy. Because of this interesting result, a second phase 2 study is underway in which Neurturin gene therapy is also targeted to the substantia nigra.

Treatment strategy	Gene(s)	Vector	Completed studies	Ongoing or Enrolling studies
Increase dopamine	AADC	AAV-2	Phase 1	Phase 1 to start in 2013
	AADC, TH, & GCH-1	Lentivirus		Phase 1 & 2 in progress
Alter excitatory activity	GAD	AAV-2	Phase 1 & 2	
Growth factors	GDNF	AAV-2	-	Phase 1 to start in 2012
	Neurturin	AAV-2	Phase 1 & 2	Second Phase 2 in progress

Other gene therapy strategies are being considered. One such study includes using human erythropoietin. This study in experimental animals showed protection against toxins that usually damage dopaminergic cells. Other therapies are using insights provided by improved understanding of genetic causes of Parkinson's disease. It is conceivable that, as our knowledge

of specific genetic defects causing Parkinson's disease improves, specific gene therapies could be developed for each individual genetic defect.

Conclusion:

Limitations in the benefit of medical and the surgical treatments of Parkinson's disease have stimulated efforts to develop new therapies. Gene therapy has distinct theoretical advantages over conventional treatment for Parkinson's disease as it might preserve or restore dopaminergic neurons through the use of growth factors or alternatively increase the availability of enzymes required for dopamine synthesis. Over the past 10 years, 3 different strategies have emerged and have been implemented in carefully designed human treatment protocols. To date, these gene therapies appear to be safe and there is some evidence suggesting benefit. Ongoing and planned phase 2 studies will identify the most promising therapies that will require further evaluation in a phase 3 study. It is hoped that gene therapies will provide improved treatment options for people with Parkinson's disease in the near future.

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