INTRODUCTION

Gene therapy is a technique with promising applications for the treatment of Parkinson’s disease. Initial clinical trials (research studies) using various types of gene therapy in patients with Parkinson’s disease (PD) are now underway or completed, and additional clinical trials are forthcoming. The aim of this article is to explain what gene therapy is and to provide information about a new clinical trial evaluating gene therapy that patients with Parkinson’s disease may wish to consider.

DEFINITIONS

Genes are chemical entities that direct the development and day-to-day function of living organisms. Humans are estimated to have about 25,000 genes, which are located on the chromosomes that are part of their cells. In humans, genes are composed of DNA (deoxyribonucleic acid), chemical building blocks that are necessary for the production of proteins. Proteins, in turn, are molecules that cause the chemical reactions that take place in the body. Thus, genes play a central part in our development, growth, and daily existence. Abnormalities in genes can directly cause some diseases or can make people more susceptible to certain diseases.

Gene therapy refers to techniques that make use of the body’s own cells and genes to produce an effect that improves health or treats a disease. Gene therapy typically involves the engineering of genes in the test tube that can then be delivered to the body to produce the desired biological effect. In some cases, the aim is to deliver the genes to cells in a specific part of the body affected by the disease, with the goal of directly replacing defective or missing genes that are responsible for the disease. This would encourage the affected cells to function in a more normal way. In another application of this direct delivery approach, the genes might be delivered to tumor cells and cause them to be destroyed or their growth to be inhibited. Another gene therapy strategy delivers the engineered genes to a site and stimulates that part of the brain to make a protein that will have a beneficial effect on neighboring cells through local effects or distant cells through the blood stream.

Because genes cannot get into cells on their own, in order for the engineered genes to get inside the cells of the targeted body tissue, they are usually inserted into a carrier. Most often, the carrier is part of a virus that has been stripped of disease-causing properties (deactivated) and used to transfer the engineered genes into the target cells. These carriers are called viral vectors. Types of viruses that have been used as vectors include...
retroviruses, adenoviruses, and adeno-associated viruses (AAV). Current human studies using gene therapy for Parkinson’s disease make use of the deactivated adeno-associated virus. This viral vector is preferred because it appears to have long-term safety, it can easily penetrate neurons (brain cells), and it does not appear to cause inflammation or an immune reaction when injected into the brain.

In PD, to get the viral vector and the gene that it carries into the part of the brain where it is needed, a neurosurgical procedure is used. This type of surgery, called stereotactic surgery, uses a metal frame that is temporarily attached to the patient’s head on the day of surgery. This technique is also used to perform deep brain stimulation surgery. Once the frame is attached to the patient’s head, a brain scan (MRI, CT scan, or both) is performed that allows the surgeon to combine the coordinates from the frame with images from the scans using mathematical software to calculate the exact starting points on the brain surface and trajectories needed to direct their instruments to the brain target of interest. In the case of gene therapy, the instrument is a very fine needle that is inserted into the brain and used to deliver a tiny amount of the gene therapy material. In most cases, multiple injections are made to ensure complete coverage of the intended area. This procedure is done with the patient asleep under anesthesia. Performing this type of surgery for the purpose of gene therapy is considered experimental, but the surgical techniques are very similar to those routinely used for other types of brain surgery. This type of surgery is generally safe, but not without risks. Anyone considering participation in a gene therapy clinical trial should speak with the medical/surgical team to understand what to expect on the day of surgery and to discuss potential risks and complications of the surgery.

DELIVERING A GROWTH FACTOR TO THE BRAIN

Parkinson’s disease is a progressive, degenerative condition. Currently, no therapies are available that definitively slow disease progression. Growth factors are naturally occurring proteins made by the body to support the growth and health of cells, particularly during early development. The theory behind using growth factors to treat PD is that a growth factor might be able to slow, halt, or reverse disease progression. Growth factors have been delivered to the brain in past experiments using infusions into the ventricular system (the fluid-filled cavities of the brain) or via a small catheter implanted into the brain target of interest that is used to deliver tiny amounts of growth factor over long periods of time. Gene transfer techniques are now being used to deliver the growth factor neurturin to the brain using the AAV vector, a compound that together is called CERE-120. This approach is being developed by Ceregene, a biotechnology company specializing in growth factors. After numerous safety studies demonstrated safety and suggested effectiveness of CERE-120 in animals, a 12-patient phase I study was conducted at the University of California, San Francisco by Dr. William Marks, Dr. Jill Ostrem, Dr. Philip Starr, and Dr. Paul Larson and at Rush University Medical Center. Encouraging results in the initial study led to the design of a larger, multi-center study that enrolled 58 patients at 8 locations in the US; UCSF was the lead team for the study. Two-thirds of patients received CERE-120 and one third of patients had sham surgery in which no treatment was delivered. Results showed no significant difference between the
active treatment and sham groups in the 12-month follow-up period defined as the main endpoint for the study but some improvement in those receiving the active treatment who were followed for 15-18 months under double-blind conditions. Later brain autopsies on two CERE-120-treated patients who died of unrelated causes indicated that CERE-120 had not traveled from the putamen to the substantia nigra—one of the main areas affected by PD—like it had in animal studies. A small study of 6 patients was then conducted to evaluate the safety of delivery of CERE-120 to the putamen and substantia nigra.

NEW GENE THERAPY STUDY OPEN

A new study that will deliver CERE-120 to the putamen and the substantia nigra will be open for enrollment in Summer 2010. Fifty two patients will be enrolled at 12 US study sites, including UCSF. The study is also being conducted at Stanford University. To be eligible, patients must

- be 35-70 years old
- have idiopathic PD, the most common type of parkinsonism
- have motor fluctuations despite appropriate medication therapy
- be on stable doses of PD medications
- have good posture and balance when PD medications are working
- meet specific criteria on a number of PD and associated symptom scales
- have no significant memory, mood or thinking problems
- have no history of prior brain surgery for PD
- be willing to delay deep brain stimulation (DBS) surgery until the blinded portion of the study is complete (1-2 years)
- be in good general health.

What is involved?

- Nine study visits during the first 12 months of study; then 6 visits during the 2nd and 3rd years of study
- Surgery to inject the gene into the brain during 1-2 day hospital stay
- Random assignment to gene transfer or sham surgery (1:1)
- On-off testing during most study visits, after 12-hour PD medication hold
- Neurological and physical evaluations
- Brain MRIs, laboratory tests, electrocardiograms, chest x-rays
- Thinking, mood and memory testing
- All out-patient visits at UCSF Mt. Zion campus, 1635 Divisadero St., San Francisco, CA
- Reimbursement available for travel and parking expenses.

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