Parkinson's Disease Society

Information Sheet

Gene Therapy for Parkinson's

What causes Parkinson's disease?
The cause of Parkinson's is not yet known. What is known is that a small part of the brain, called the substantia nigra, that controls movement, loses many of its nerve cells (also known as neurons). These nerve cells use a chemical messenger, known as dopamine, to send messages to other parts of the brain to co-ordinate movement. The messages eventually reach the muscles via the spinal cord.

Because there is a shortage of these dopamine-containing cells, the symptoms of Parkinson's appear: tremor, rigidity and slowness of movement.

Much of the current medical research into treatments for Parkinson's (including gene therapy) is concerned with trying to replace this lost dopamine by using drugs that mimic its actions (bypassing the need for dopamine itself) or with preventing the remaining nerve cells from being broken down so that they remain more effective.

What is gene therapy?
Gene therapy is a new approach to treating medical conditions, which can be described as the use of genes as drugs. It works by introducing normal genes into people with certain disorders to overcome the effects of defective genes that may cause or have a part to play in the development of their condition. Gene therapy can also be used to treat disorders where the genetic cause is not known, or may not be caused exclusively by genetic defects, such as Parkinson's.

Is Parkinson's inherited?
In most cases, Parkinson's is not thought by researchers to be directly inherited. However, there are a small number of families where there does seem to be a higher incidence. Research has shown that there are some genetic mutations (changes in the composition) of genes found in these families, and specific proteins produced by the genes have also been identified, which seem to have some causal link to Parkinson's.

This genetic susceptibility, combined with other factors (such as viruses or environmental agents), may make these people more likely to develop the condition.

It is important to note that a condition does not have to be caused by genetic factors for gene therapy to be a potential treatment. In the case of Parkinson's, gene therapy could be used to prevent the death of nerve cells and also to promote the regeneration of those in the early stages of cell death.

Why is gene therapy being developed as a new treatment strategy for Parkinson's?
During the early stages of Parkinson's, drugs such as levodopa and dopamine agonists can be very effective in treating the clinical symptoms, although they do not halt or slow down the rate of nerve cell death or disease progression. However, with long-term use, there is a tendency for the drugs to become less effective and for potentially disabling side effects to occur. The symptoms of Parkinson's also tend to become worse as the condition progresses. This reduction in drug effectiveness is due to a combination of the progression of Parkinson's and the person's altered response to the drugs.

There are some drugs available to treat the later stages of Parkinson's, and more are in

development. However, although these provide relief from the symptoms, they do not offer a cure. Researchers continue to look for new, more effective treatments for Parkinson's, and one such approach is termed gene therapy.

How will gene therapy be used to treat Parkinson's?

Using gene therapy approaches, scientists have aimed to deliver various kinds of gene products directly to the affected brain areas for the treatment of Parkinson's. There are two primary classes of products used:

Neurotrophic factors, such as GDNF (glial cell line derived neurotrophic factor), are powerful promoters of the growth and survival of these cells, and they can protect neurons from further damage. Direct delivery of these molecules into the brain has been attempted in trials with people with Parkinson's, but these trials have shown that it can be difficult to maintain consistently high levels of the factors in the part of the brain where they are needed. Furthermore, some significant side effects were reported for this agent. One aim of gene therapy is to allow the continuous production of these growth factors within the brains of people with Parkinson's.

Proteins that increase the levels of dopamine production. An alternative to administering levodopa or dopamine agonists is to increase the capacity of the nerve cells to produce their own dopamine. Certain enzymes, including tyrosine hydroxylase and dopa decarboxylase, play a key role in the process of dopamine manufacture. These cannot be delivered by simply injecting the protein, as it does not readily enter the cell. Recent research evidence suggests that other proteins, such as biopterin, can also help to make the process of dopamine generation even more efficient. The gene therapy technique would allow the genes for these proteins to be delivered inside the appropriate cells. This would create a new factory for making dopamine in the brain.

How can therapeutic genes be delivered into the brains of people with Parkinson's?

In order to transfer therapeutic genetic material into the brains of people with Parkinson's, researchers are using a number of viruses, including the adenovirus and lentivirus. Viruses are the smallest known type of infectious agents. They can also be used as carriers of genes around the body to a particular place. Before they can be used as carriers, the ability of the virus to cause infection has to be stopped, so they can carry the therapeutic materials around the body safely.

Genes encoding therapeutic compounds (such as those encoding neurotrophic factors or proteins that manufacture dopamine) can be inserted into these viruses. The virus will then transport this material to the place in the brain where the compounds are needed, either to protect the neurons from further damage or to promote the generation of dopamine that is in short supply in the brains of people with Parkinson's. The therapeutic viruses will be injected directly into the targeted brain areas, where they will release the therapeutic material. They will not spread around the body, like a normal virus, because the capacity to do so has been completely eliminated by the researchers.

These viruses have been tested in several animal models of Parkinson's and the trials have so far shown that it may be possible to prevent death of the neurons and to slow, halt or reverse the associated Parkinson's symptoms.

What further research needs to be done to make gene therapy a treatment for Parkinson's?

Although the results described above are very encouraging, there are several issues that need to be resolved before gene therapy can become a successful treatment for neurological conditions in humans, including Parkinson's. These include ensuring that:

- the therapeutic materials remain active in the brain for a long time, hopefully for many years
- the therapeutic materials will remain in those areas within the brain where they are needed
- it is possible to regulate how much of the therapeutic material is present at any one time to achieve the greatest benefits for the person with Parkinson's
- the viruses are safe

So far, research has shown that it is possible to achieve very long, persistent and widespread distribution of therapeutic materials within the brain, and the researchers can also very accurately regulate how much therapeutic material is being delivered. Using the new type of safer viruses that do not contain any viral genes that could cause an infection, it should be possible to achieve at least one year of production of therapeutic factors within the brain. It is also important that these viruses should not cause adverse effects while achieving high levels of therapeutic material production within the brain.

Are there any risks associated with gene therapy?

All therapies, of course, have risks – including gene therapy. Risks associated with gene therapy include inflammation in the brain, and side effects associated with long-term exposure to the gene products within the central nervous system. These side effects are currently being investigated as part of the research.

Who will be suitable for gene therapy?

It is unlikely that gene therapy will be suitable for everyone, and detailed studies will be required to identify those for whom it will be most beneficial. It is likely to be used to treat people in the early stages of Parkinson's whose nerve cells are still alive, people whose symptoms are not well-controlled using currently available medications, or those with severe side effects such as dyskinesias (involuntary movements).

Gene therapy is unlikely to be used for people who have severe depression, confusion or psychosis.

Gene therapy will be useful as a treatment for Parkinson's, whether or not a genetic cause led to or contributes to their disease. Gene therapy uses genes as drugs, not necessarily as replacements for faulty genes. Just as classical drug treatment works independently of the cause of disease, so will gene therapy.

When will gene therapy be available as a treatment?

Gene therapy is not yet available as a therapeutic option for people with Parkinson's and is still in the early stages of research. There are currently several trials taking places in humans for new gene therapies for Parkinson's. These trials are at different stages of development and while initial results appear to be encouraging, one of the trials did not

show any beneficial effects. Therefore, much more research needs to be carried out before we can say if, or when, this will be available as a treatment for people with Parkinson's.

What does the future hold for gene therapy and Parkinson's?

Gene therapy offers the possibility of changing the natural progression of Parkinson's. So far, all other treatments have aimed at modifying the symptoms. With gene therapy it is hoped that the progression of Parkinson's will eventually be halted and a potential cure(s) found.

Where can I get more information on gene therapy?

The Parkinson's Disease Society's (PDS) quarterly magazine, *The Parkinson,* has a regular section on research, which includes regular updates of any research that the PDS funds. Any further developments in gene therapy will be reported in future issues.

The Society also produces the twice-yearly research magazine *Progress*, which looks into PDS-funded research in more depth.

The PDS has a research programme and anyone wanting more information about this work should contact the PDS Research Department at the PDS London office (research@parkinsons.org.uk).

The PDS also has a special interest group called **SPRING** (Special Parkinson's Research Interest Group) for people interested in medical research. They can be contacted at:

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WE MOVE (Worldwide Education and Awareness for Movement Disorders) is an American organisation that aims to provide information about clinical advances, treatment and research into movement disorders, including Parkinson's. It has a database called **E-MOVE**, which has several papers on gene therapy and Parkinson's. The website address for **E-MOVE** is: www.wemove.org/emove

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Glossary

Carriers of genes – viruses or other agents used to transport genetic material to the appropriate part of the body.

Genes – the biological units of inheritance. There are approximately 35,000 in the genetic make up of a human being and they are arranged on 23 pairs of chromosomes within the cell. A particular gene has a specific role in the workings of a cell. Some diseases are caused by faulty genes that do not work properly.

Gene encoding – the instructions contained in chemical form within the genes that specify the activities of the cells. These can be altered for therapeutic purposes as part of gene therapy.

Intravenous administration – administration of a drug into a vein.

Mutation – process by which a gene undergoes a structural change.

Neuron – another name for a nerve cell. The nervous system contains billions of neurons which act in various combinations to perform all functions of human life.

Proteins – large molecules in the body that have a variety of functions, including making up the structure of many body tissues, enzymes that promote biochemical reactions in the body, and hormones.

Neurotrophic factors – factors that help keep nerve cells alive.

Virus – the smallest known type of infectious agents. Viruses can also be used as carriers to transport therapeutic materials, such as adapted genes, around the body.

Parkinson's
Disease Society

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