

Reflection and Reaction

Gene therapy for Parkinson's disease: do we have the cure?

by Alim Louis Benabid

The discovery of levodopa is widely acknowledged as a therapeutic miracle that has changed the lives of millions of people with Parkinson's disease. However, just as every coin has a reverse side, levodopa has dyskinesias, which occur after 5–10 years and decrease the benefits of treatment. Additionally, levodopa does not alter the course of Parkinson's disease. During the past five decades, pharmacological and surgical researchers have aimed to develop disease-modifying treatments. Neural grafts and, more recently, gene therapy offer the potential to cure Parkinson's disease by implantation of dopamine-producing neurons into the striatum or by changing the genetics of neurons involved in the damaged circuitry. Although grafts for Parkinson's disease have been tested in people for three decades now, they are still considered experimental because they have not as yet provided therapeutic benefit. Gene therapy might bring some hope. In this issue of *The Lancet Neurology*, Marks and colleagues¹ report the results of “the first double-blind, controlled phase 2 trial of a gene therapy for Parkinson's disease”. Is this finally the long-awaited cure? Present approaches to gene therapy for neurodegenerative diseases involve one of three types of gene: those that alter the function of networks by changing the neurotransmitter profile of cells (e.g., transfection of the *GAD* gene into the glutamatergic subthalamic nucleus to change it into a GABAergic structure);² those that encode dopamine-synthesizing enzymes, to restore their missing products; and those that encode growth factors, which slow down the neurodegenerative process. All three approaches originate from basic research, have been tested in animal models,^{3–5} and are now being tested in clinical trials.^{2,6,7} Marks and colleagues' approach involves growth factors: an adeno-associated vector (AAV) carrying the gene for neurturin was injected into the striatum. The rationale is that neurturin, a growth factor that can alter the neurodegenerative processes that lead to death of dopaminergic neurons in the substantia nigra pars compacta in animal models,⁴ will protect these neurons in patients, partly through retrograde transport of the protein from the striatum to the nigral neurons. The results of the trial only partly support this hypothesis: the 38 treated patients and the 20 patients who received sham surgery did not differ with regard to the primary endpoint—the motor subscore of the unified Parkinson's disease rating scale in the practically defined off state at 12 months. However, the treatment group (n=19) did show an improvement compared with the sham surgery group (n=11) at 18 months (least squares mean change from baseline to 18 months –11.96 in the AAV2-neurturin group compared with –4.34 in the sham surgery group; p=0.023). Several issues must be resolved before one can celebrate the victory of a gene therapy for treatment of Parkinson's disease. Is gene therapy better than present treatments? What are the safety issues and are they acceptable? How does the gene therapy approach presented in Marks and colleagues' paper compare with those used in other studies? To be the treatment of the future for Parkinson's disease, gene therapy must cure the disease. The results of this and other preliminary trials of gene therapy in Parkinson's disease have been anxiously awaited: will the clinical application of gene therapy be more successful than that of neural transplantation? To be a viable treatment option, gene therapy should also provide as much benefit as therapeutic alternatives currently available, such as deep brain stimulation. The advantage of gene therapy is certainly its potential to cure, but this has to be further proven. The late appearance of the benefit of treatment compared with sham surgery in the present trial¹ might be due to the time required for the transfected genome to start to function, but whether this late improvement will continue and surpass that of alternative treatments, or will stabilize and then progressively disappear, remains to be seen. Beneficial clinical effects must be substantiated by and associated with positive results of functional studies, for example from

fluorine-18-labelled dopa PET scans. Careful and long-term follow up of patients from the present trial¹ should also answer these questions and is a necessary commitment in light of the risks taken by the patients who received AAV2-neurturin treatment. The safety issues of gene therapy have not yet been solved, as Marks and colleagues acknowledge.¹ The possible risk of tumor induction must be carefully documented over time. The pre-existing glioblastoma that was reported in one patient seems to have been independent from the gene transfer therapy but, in principle, one cannot rule out that focal delivery of growth factors to a brain that has a neoplasm might stimulate the cancer cells. Side-effects that have been reported in clinical trials of integrated retroviral vectors for uses outside the brain might jeopardize the development of neurological gene therapies.⁷ Sham surgery is always a matter of ethical debate. Limiting the sham operation to the external layers of the cranial envelope makes it more acceptable because the dura is not opened, but some patients did experience minor side-effects from the procedure. The safety of sham surgery was nevertheless justified a posteriori by the parallel improvement of the two groups during the first 12 months after treatment.¹ This finding also calls into question the nature of the placebo effect, suggesting that it might be at least partly biological rather than just psychological. What are the respective benefits of the present gene therapy approaches? The growth factor approach has potential protective and regenerative properties, as reported in findings from in vitro and animal studies.⁴ The trial by Marks and colleagues¹ brings a little evidence that this treatment might cure Parkinson's disease, and the suggestion that AAV2-neurturin is transfected directly into the substantia nigra pars compacta in future studies is interesting. The restorative gene therapy approach, using delivery of three synthesising enzymes through a single vector, is more attractive than the single-gene approach used by Marks and colleagues because it should restore dopamine synthesis. But, as for all other approaches, we await results from clinical trials.⁵ The findings of Marks and colleagues¹ provide the first clinical evidence of a clinical benefit of gene therapy in Parkinson's disease; these results will serve as a starting reference that it is hoped will be exceeded in future trials.

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I declare that I have no conflicts of interest.

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