Review Article

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# Combination of cell transplantation and glial cell line-derived neurotrophic factor-secreting encapsulated cells in Parkinson's disease

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**Abstract:**

A major limitation of cell transplantation for Parkinson's disease (PD) is the mediocre survival of the grafted cells. Facilitating graft survival may improve the functional outcomes of the transplanted cells. Here, we discuss our observations that combination of rat fetal ventral mesencephalic (VM) tissue and encapsulated cells that secrete glial cell line-derived neurotrophic factor (GDNF) enhanced graft function in an animal model of PD. We described significant 2-fold increase in the number of tyrosine hydroxylase immunoreactive (TH-ir) cells per graft, as well as 1.7-fold and 9-fold increments in TH-ir fiber outgrowth into the host brain and toward the capsule with combined transplants and GDNF capsules as opposed to the VM transplants and mock-capsule group. These findings demonstrate that encapsulated GDNF-secreting cells improve graft survival that may optimize functional benefits for the treatment of PD.

**Keywords:**

Dopamine, stem cells, transplantation, neurotrophic factor, neurodegeneration

## Introduction

Parkinson's disease (PD) is characterized by degeneration of the nigrostriatal region with a consequently reduction in dopamine. Pharmacological treatment currently available reduces the symptoms of the disease but is associated with severe side effects.[1,2] Alternative strategies have been investigated including the application of neurotrophic factors and the transplantation of dopaminergic (DAergic) neurons with promising results.[3-5]

## Current Status of Treatment for Parkinson's Disease

Transplantation of fetal nigral tissue has been reported to be safe and to improve quality of life in a subpopulation of PD patients.[6-9] Hence, further advances in this field should be done including the handling of the fetal donor tissue and patient selection in clinical trials.[7,10-12] In this contest, even though the organotypic ventral mesencephalic (VM) cultures are widely used, the improvement of the DAergic neurons' survival is still a challenge.[13,14] It has been demonstrated that a reduction in trophic support in the host brain is linked with a poor survival, growth, and function of transplanted DAergic neurons.[15] In addition, cell line-derived neurotrophic factor (GDNF) can promote survival and differentiation of DAergic neurons.[12,16,17] Therefore, these findings support the hypothesis that adding growth factors in cell transplantation could be a potent strategy for the treatment of PD.[18-20] In this regard, it has been tried to genetically modify cells to produce neurotrophic factor fibroblast growth factor 2.[21] However, the direct contact with the DAergic-transplanted cells is needed to improve the graft function.[21] Another

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strategy to improve the engraftment is the pretreatment of DAergic neurons with GDNF tested in animal models and in a pilot clinical trial.[22-24] Nevertheless, there is no correlation among clinical trials testing the delivery of GDNF in PD patients.[12,25] The reasons could be due to a number of technical and the activity of neurotrophic factors in pathological conditions.[4,12,25] In particular, the low ability of the neurotrophic factor to cross the blood–brain barrier and the presence of their receptors spread throughout the brain, with the consequence to induce side effects, are the main issues that should be investigated.[17] And therefore, the selective targeting of the transplanted cells is a key aspect in cell therapy of PD. The survival and sprouting of grafted DAergic neurons has been improved with co-transplantation of engineered GDNF-releasing cells in PD animal model.[26-28] Even though cell bioengineering allows improving the graft, the risk of rejection of transplanted cells and tumor formation are critical issues of this strategy.[27] Conversely, the use of a porous polymer membrane to encapsulate the neurotrophic factors-producing cells is immunocompatible and safe in human up to 2 years.[29,30] In addition, it has been demonstrated that the implanted GDNF-releasing capsules 1 week before the VM tissue transplantation improved graft function.[27] However, further investigation should be conducted. In the present article, the simultaneous transplantation of rat fetal nigral tissue and polymer-encapsulated myoblasts genetically modified to produce GDNF has been studied in a 9-week period to test its effects on the survival and function of transplants.[31]

## Combined Fetal Cell Grafts and Encapsulated Glial Cell-Derived Factor-Secreting Cells

A significant increase in the number of tyrosine hydroxylase immunoreactive (TH-ir) cells per graft (2 folds), a tendency for a larger graft volume along with a higher TH-ir fiber outgrowth into the host brain (1.7-fold) and toward the capsule (9-fold), has been observed in hemi-parkinsonian rats grafted with VM transplants and GDNF capsules compared with VM transplant and mock-capsule group. In addition, a significant functional recovery was associated with simultaneous VM transplants and GDNF capsules after 4 weeks of the transplantation, while no behavioral recovery was observed with the GDNF-capsule-only treatment. Moreover, no significant variation in the number of surviving TH-ir neurons and graft volume was observed between the experimental groups.

## Enhancement of Graft Survival and Function via Combination Therapy

For the transplantation, each animal received half of a VM to provide about equal amounts of DAergic neurons in the grafts, a validated approach established by the same research group.[27,28,32] The capsules were well tolerated as demonstrated by the body weight of the animals that was not altered after the treatment. Opposite to other observation, the group treated with GDNF-capsule-only has not shown behavioral recovery.[33] However, this contrasting result is probably due to the animal model employed because the medial forebrain lesions can result in a more severe denervation of striatum compared to intrastriatal 6-OHDA injection used by Date *et al*.[33,34] Another reason may be the timing of the GDNF-releasing capsule implantation. Indeed, the authors injected the GDNF-releasing capsules in an advanced stage of the disease (13 weeks), while Date *et al*. in an earlier phase (2 weeks).[33] Nevertheless, a moderate sprouting of the remaining DAergic striatal fibers, even though not such to improve the functional recovery, cannot be excluded. Notably, the results of Perez-Bouza *et al*.[31] support previous evidences that the functional recovery is dependent on DAergic cell survival and integration in the host brain.[6,35] Indeed, the rate of surviving TH-ir cells with GDNF treatment is consistent with previous studies.[27,36] Interestingly, the treatment with GDNF correlated with the increase of fiber outgrowth, especially between the graft and the capsule, also suggesting a GDNF gradient into the host brain, unlike to what has been previously reported.[28] Despite the mechanism of GDNF diffusion from the capsule which has not been investigated in the present study, it has been reported that GDNF can diffuse about 1.5 mm without altered behavior. Other studies have shown that GDNF-ir reached 2–3 mm in rats and a radius of 11 mm from the infusion site in monkeys.[37-39] The amount of GDNF for therapeutic purposes should be further investigated because of the side effects reported.[8,40-42] In the present study, the behavioral recovery has been reported after only 4 weeks by using rat VM tissue, while a later recovery after 12 weeks has been observed by using human VM tissue, suggesting a difference on the developmental rate between the species.[39] Another critical aspect that should be considered is the period of exposition to GDNF. In the present work, the uncharged rotational asymmetry after 4 weeks suggests that a shorter exposition time of VM tissue to GDNF should be enough accordingly to previous observations that a temporary or shortly thereafter delivery of GDNF is effective compared to a delayed application.[10,43] These results suggest that genetically modified encapsulated cells releasing growth factors might support the maintenance of a neuronal phenotype and/or maturation of transplanted neural stem cell-derived cells.[44,45] Moreover, the pretreatment of VM tissue has not affected the volume and number of TH-ir cells after transplantation compared to the cultured grafts, with a consequently similar pattern of behavioral recovery among the groups, supporting the hypothesis

that the pretreatment may improve cell transplantation approaches for PD. In addition, in agreement with previous observations, GDNF pretreatment increased fiber outgrowth, but did not enhance the survival of graft DAergic cells, suggesting that the duration of pretreatment, longer in the earlier study, may affect the outcome.[23] Notably, the monitoring of dynamic changes of the graft at histological level after transplantation is not investigated in this work and therefore, a stabilization of intrastriatal levels of GDNF at long term cannot be excluded.

## Conclusion

Our findings suggest that pretreatment with neurotrophic factors, such as GDNF and NT-4/5, might improve the transplantation methodology for PD patients.[46] In the clinic, the challenge of harvesting fetal tissue may present as a factor, but the availability of nonfetal tissues such as induced pluripotent stem cells may circumvent this logistical issue.

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### Conflicts of interest

There are no conflicts of interest.

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