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Neurotransplantation: the Time Has Come?

S. N. Illarioshkin*

Research Center of Neurology, Moscow, 105064 Russia
**e-mail: snillario@gmail.com*

Abstract—Problems in curing disorders of the brain are caused by several characteristic features of the nervous tissue, such as postmitotic nature of neurons, their limited reparative potential, significant energy dependence, etc. Because of special vulnerability and extremely high specialization, neurons are very sensitive to the action of any pathological factors, while existing possibilities of their trophic and metabolic support are scanty. Therefore, the creation of new reparative strategies, including substitutive cell technologies, is immediate task in neurology. Neurodegenerative disorders, Parkinson's disease (PD), Huntington's disease and others, are an "ideal" model for elaborating such strategies. As main motor symptoms of PD are related to degeneration of the dopaminergic nigrostriatal pathway, treatment of these patients, theoretically, may be based on transplantation of dopamine-producing neurons into the striatum. In the paper, analyzed are the results of many-year experimental (on models of parkinsonism) and preliminary clinical trials of neurotransplantation with the use of fetal tissues (dopaminergic cells of the ventral midbrain) and dopaminergic neurons differentiated from embryonal stem cells and induced pluripotent. Newest scientific achievements in this field, improvement of cell protocols and successful resolving of a number of technical and medical problems allow saying that neurotransplantation becomes clinical reality just before our eyes.

Keywords: neurotransplantation, dopaminergic neurons, fetal cells, induced pluripotent stem cells, Parkinson's disease

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Nervous system diseases represent one of the most complex problems due to several properties of nervous tissue that makes it difficult to treat. Differentiated neurons are post-mitotic cells with limited repair ability and are incredibly energy-dependent due to the complexity of their function, such as axonal transport, maintenance of membrane action potential and generation of nerve impulses, dynamic organization of synaptic contacts, etc. [25]. Because of their special vulnerability and high specialization, neurons are very sensitive to any pathological factors (hypoxia, excitotoxicity, oxidative and proteolytic stress, etc.), and their existing trophic and metabolic support is very limited.

To date, there are no drugs with a definite clinical neuroprotective effect, despite the results of numerous experimental studies supporting the neuroprotective effects of several compounds [22, 25]. New reparative strategies therefore must be developed. Great hope is being placed on cell replacement technologies, including neurotransplantation, to restore brain function lost due to acute damage or chronic progressive diseases of the nervous system [43].

One of the chronic neurodegenerative diseases in which cell replacement therapy is being used to compensate for the central dopaminergic deficit is Parkinson's disease (PD) [2, 38, 50]. The motor symptoms in PD are due to the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain (A9 neurons are the most susceptible subpopulation) and degeneration of the nigrostriatal pathway, resulting in a significant (>80%) reduction in the striatal dopamine level [51]. For this reason, leading treatment approaches have been replacement therapy with levodopa (a biological precursor of dopamine), prescription of dopamine receptor agonists and other correctors of central neurotransmitter imbalance, as well as stereotactic surgery to modulate the neural network activity of basal nuclei [48, 51]. However, increasing complications from long-term therapy and the appearance of symptoms resistant to dopaminergic stimulation have presented doctors with new and often intractable problems. In addition, modern treatments of Parkinson's disease do not prevent progression of the neurodegenerative process [51].

Considering the comparative limitations of the neuroanatomical defect responsible for motor disorders in PD, transplantation of dopamine-producing neurons into the striatum can be considered as a basic treatment alternative. It is aimed at restoring nigrostriatal innervation as well as the lost dopamine level in the striatum (through the additional trophic effect), to prevent or slow down the degeneration of the surviving neurons [38].

It was shown in the late 1970s and the 1980s that embryonic dopaminergic neurons of the ventral mid-

brain, transplanted into the brain of rodents and lower primates with PD models, can survive this procedure and reinnervate the recipient's striatum [9, 12]. There was even partial recovery of the lost motor functions.

The first clinical studies of cell therapy to treat PD, involving more than 400 patients, were conducted in the late 1980s at Lund University in Sweden [14]. Foetal cell material rich in dopaminergic neurons and obtained from the midbrain of aborted human embryos was implanted into the caudate nucleus and/or putamen of patients with PD with a positive clinical effect achieved in some cases, correlating with restoration of the striatal dopamine levels and an improvement in the quality of life [40, 53]. In the 1990s, this neurotransplantation protocol was investigated as part of the European multicentre NEKTAR study, which included Russian scientists [7]. However, the results of two NIH-sponsored double-blind placebo-controlled trials were disappointing: apart from a lack of a convincing clinical effect, foetal neurotransplantation was accompanied in many patients by severe graft-induced dyskinesia [24, 46]. Unacceptable complications, in the form of severe dyskinesia, were confirmed by retrospective analysis of patients with PD included in an open-label study [28], which led to the temporary cessation of such surgeries.

Despite the forced break in clinical studies of foetal cell transplantation in patients with PD, a large-scale study of these complications was commenced in the early 2000s, which marked the beginning of the modern era of researching regenerative cell therapy [51]. As a result of the studies, a hypothesis was made that the risk of postoperative hyperkinesia may be reduced by minimizing the number of serotonergic neurons in the transplant [18] and by selecting patients with PD without previous levodopa-induced dyskinesia [37]. Another problem, which has been widely discussed in the literature, was autopsy findings in operated patients, showing that Lewy bodies appear in the transplanted foetal cells years after surgery; i.e., the owner's 'diseased' neurons transmit the α-synuclein pathology to external healthy cells [13]. In neurons implanted into the brains of patients with PD, there is induction of the parkinsonian neurodegenerative process by a mechanism similar to prion disease, which is confirmed by decreased expression of tyrosine hydroxylase (TH) and dopamine transporter (DAT) in these cells [13]. However, this process is slow and can disrupt transplant function only after about 15 years, which, according to consensus, justifies continuing clinical studies and should not cast doubt on the possibility of patients obtaining a sufficiently persistent clinical improvement [51]. This has been confirmed by two unique clinical observations of patients with PD, in whom a persistent clinical effect and improvement in striatal dopamine metabolism on PET persisted for 15–18 years after transplantation, and both patients did not receive any antiparkinsonian drugs throughout the whole postoperative period [32].

After a long break, TRANSNEURO, a new open-label clinical trial of foetal dopaminergic neuron transplantation into the striatum was begun in 2015, under the auspices of the EU Special Research Group. This study involves a detailed assessment of the effects of neurotransplantation in 20 patients with relatively early-stage PD and without drug complications [50], followed by possible recruitment of up to 100 patients. According to the published press releases, all the surgeries in the first phase of this project have already been carried out, and these patients are being now carefully monitored. The purpose of this important phase is to assess whether graft-induced dyskinesia can be avoided and to prepare a foundation for future stem cell research (see below).

In addition to postoperative dyskinesia, significant disadvantages of foetal neurotransplantation include the limited amount of tissue for transplantation, as well as serious immunological (donor/recipient incompatibility) and ethical (use of human abortive material) issues [10, 11]. Therefore, experimental and clinical attempts have been made for a long time to transplant other types of cells into the brain, including catecholamine-releasing chromaffin cells of the adrenal cortex, dopaminergic cells of carotid bodies, mesenchymal stem cells, retinal dopamine-containing cells, olfactory epithelial progenitor cells, and xenotransplants from various animals, but with no significant effect [1, 26, 27, 38, 41, 47]. To date, there is no evidence base for any of these cell therapy methods in PD [47]. A serious alternative is embryonic stem cells (ESCs) derived from human blastocysts and capable of differentiating into dopaminergic neurons. Transplantation of these neuronal ESCs has been effective in rodent PD models [2, 51]. However, a number of obstacles exist for their clinical use, primarily the need to manipulate human embryos.

A new unique source of cell transplants containing autologous dopaminergic neurons has been found through the discovery of induced pluripotent stem cells (IPSCs). They are obtained by reprogramming available somatic cells (e.g., fibroblasts), using their expression of peptide pluripotency factors [54], with the IPSCs then differentiating in vitro into neurons as part of the developed protocols [2]. It has now been shown that dopaminergic neurons differentiated from IPSCs correspond to the morphology and function of native dopaminergic neurons, confirmed by their intrastriatal transplantation in rodent and lower primate models of PD. The criteria for this correspondence are basic histological, biochemical and physiological parameters, such as the survival rate of transplanted neurons, the intensity of the transplant's neuritic growth, the formation of a diffuse network of dopaminergic terminals in the striatum and their release of dopamine, parameters of their bioelectrical activity, as well as restoration of lost motor functions in animal models of PD [2, 10].

The first attempts to transplant dopaminergic neurons differentiated from human IPSCs into experimental animals were made in the last decade in rat models of PD [16, 30, 52, 55]. There was partial restoration of motor and behavioural functions after these neurons were transplanted into the striatum. The transplanted precursor stem cells had a positive effect, apparently by not only replacing the recipient's lost cells but also through trophic support, immunomodulation and stimulation of neuronal plasticity [2]. It was later shown that transplants with a large number of autologous dopaminergic neurons differentiated from IPSCs, which survived in the brain of a Crab-eating macaque with PD model for up to 2 years, reinnervate the striatum and improve motor function without the use of anticancer drugs and immunosuppressants [29].

Functional precursors of dopaminergic neurons, in addition to being generated through transformation into IPSCs, can be obtained by direct conversion from human fibroblasts, bypassing the pluripotent stage [17], which may be of considerable interest for clinical practice. It has been shown that dopaminergic neurons, differentiated from mouse fibroblasts, retain a stable phenotype in vivo and in vitro without first being reprogrammed into IPSCs, and having been transplanted into a denervated rat striatum, functionally integrate into the brain tissue, and this integration is accompanied by intensive axonal growth [21]. In addition, such transplanted neurons possessed electrically excitable membranes, generated synaptic potentials, released dopamine and contributed to eliminating motor disorders in experimental animals [21].

The work of Avaliani et al. (2014) provided serious support for the possibility of forming functional synaptic connections between transplanted dopaminergic neurons, differentiated from human IPSCs, and the recipient's brain tissue. It described in detail the functional properties of these neurons, transplanted into organotypic explants of the hippocampus in vitro and into the adult rat brain [8]. Before transplantation, IPSCs were transformed into long-term selfselectively damages dopaminergic neurons. The work was performed on male Wistar rats aged 3–4 months ($n = 12$), and the Any-maze video tracking system was used to record and analyse animal behaviour in the experiments.

By the end of Week 4 after 6-OHDA administration, the animals demonstrated a steady increase in rigidity, hypokinesia, ptosis and other motor symptoms, a sharp decrease in motor activity in the open field test (Fig. 1a) and typical apomorphine-induced rotational behaviour, indicating PD development. Next, differentiated dopaminergic neurons obtained from human IPSCs, were stereotaxically transplanted into the striatum of rats in the renewing neuroepithelial-like stem cells (It-NES cells), which are neural progenitors of primary GABAergic neurons. Six weeks after transplantation into the explant, neurons differentiated from It-NES showed properties characteristic of mature neurons, such as generation of membrane tetrodotoxin-sensitive sodium currents, action potentials and spontaneous and induced postsynaptic currents, indicating the presence of functional afferent synaptic inputs. Thus, there was strong evidence that neurons differentiated from IPSCs can achieve significant morphofunctional integration with the recipient's nervous tissue.

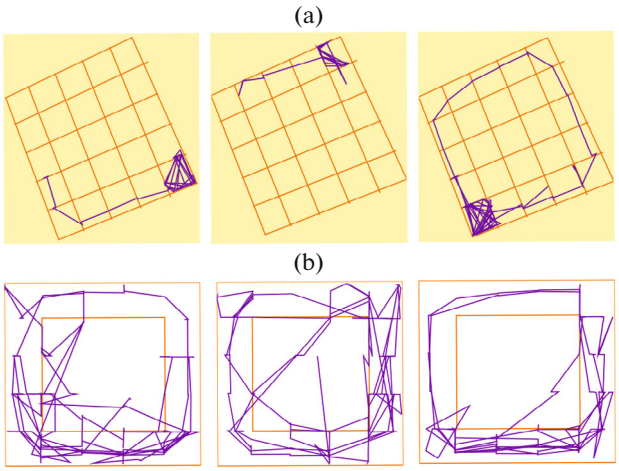

Fig. 1. Examples of the "open field" tracking of rats with induced parkinsonism (a) and of the same animals 33 days after striatal transplantation of dopaminergic neurons (b).

In our own research, conducted by the Research Centre of Neurology in conjunction with the Institute of Molecular Genetics and the Vavilov Institute of General Genetics of the Russian Academy of Sciences, the possibility of neurotransplantation was examined on a toxic model of PD in rats, using dopaminergic neurons derived from human IPSCs [3, 4, 6]. PD modelling was carried out by administering the neurotoxin 6-OHDA into the rat substantia nigra, which main group ($n = 8$), as a cell-containing suspension with a concentration of 1×10^6 in 10 μL of saline solution. Animals in the comparison group ($n = 4$) were injected with human fibroblasts according to the same scheme. For immunosuppression, all recipient rats received daily injections of cyclosporine (15 mg/kg).

Three weeks after neurotransplantation, all recipient rats showed a stable and clear increase in motor activity in the open field test, which was maintained during subsequent observation (Fig. 1b). There was also a significant decrease in rigidity and ptosis. Throughout the whole experiment (up to 16 weeks of observation), motor activity remained statistically significantly higher compared to activity recorded before neurotransplantation (Fig. 2). By the end of Week 6 of observation, muscle rigidity, hypokinesia, postural disorders and ptosis had completely regressed in the operated animals, and these positive changes, as well

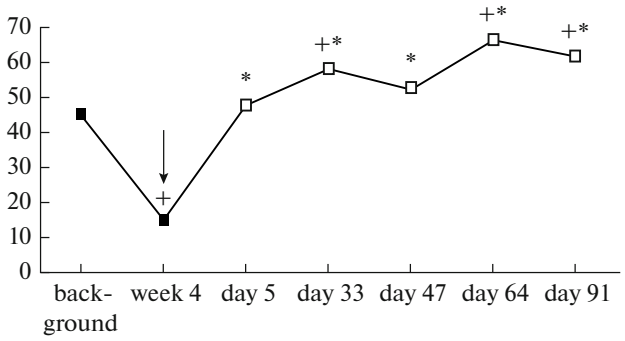

Fig. 2. Mean changes of "open field" motor activity in rats with parkinsonian syndrome during a long period after striatal transplantation of dopaminergic neurons. Y-axis: the number of crossed squares. Arrow indicates the moment of implantation of dopaminergic neurons. +—differences are significant compared to the background; *—differences are significant compared to the level of motor functions in maximal parkinsonian syndrome (4 weeks after toxin injection).

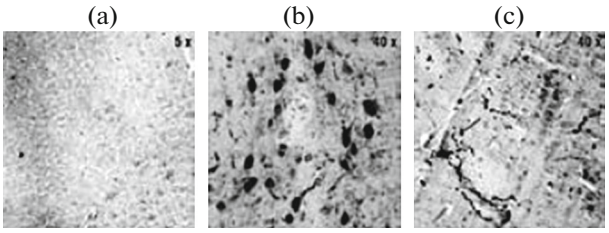

Fig. 3. Identification of TH in the graft. (a) Dopamine denervation of the striatum on the side of neurotoxin-destroyed substantia nigra. (b) TH-positive cells in the striatum on week 4 after neurotransplantation. (c) Distribution of the TH-positive processes in the marginal zone of the graft on week 6.

as an increase in motor activity, remained for the 16 weeks of observation. The rotational behaviour observed in the first apomorphine test (after toxin administration) was statistically significantly reduced in the second test (4 weeks after neurotransplantation). The transplantation of fibroblasts into the caudate nuclei of the comparison group did not have a pronounced effect on animal behaviour.

At different times after neurotransplantation (3, 5, 7, 14, 32 days and 4 months), immunohistochemistry was conducted to measure TH and DAT expression, which are markers of dopaminergic neurons, as well as human nuclear antigen (HNA), to detect the transplanted cells. The initial unilateral damage to the substantia nigra after intranigral administration of 6-OHDA was confirmed by a sharp decrease in TH expression in the ipsilateral striatum (Fig. 3a).

After neurotransplantation, cells containing both the human nuclear antigen and dopaminergic markers were detected in the transplant on serial sections, and the TN and DAT-positive cells had the same location (Fig. 3b). Single dopamine neurons, not expressing HNA and corresponding to the rat's own striatal neurons, were observed outside the transplant area. By Day 5–7, the transplant area was surrounded by a glial shaft composed of rat astrocytic cells. The number of HNA-positive cells in the transplant area decreased significantly in the first week after administration (by 46% on average), after which the transplant size remained stable at 0.06–0.1 mm^3, and the total number of human cells detected a month after administration was up to 150000. The number of dopaminergic neurons in the transplants was less than 10% of the detected HNA-positive cells 3–4 weeks after administration, but these transplanted dopaminergic neurons remained viable in the striatum of recipient animals throughout the follow-up period (up to 4 months). Starting from Day 7 after surgery, TH-positive processes of the transplanted neurons were observed in the graft area, and processes were detected outside the transplant area, up to 1 mm from its border (Fig. 3c), after 32 days and 4 months, which suggests the formation of contacts between transplant cells and the striatal neurons of experimental animals.

This study confirmed the possibility of correcting motor disorders in animals with the 6-OHDA model of PD, through repopulation of dopaminergic neurons, the source of which may be IPSCs obtained from somatic cells.

It is worth emphasizing that the strategy of using dopaminergic neurons converted from IPSCs for cell therapy in PD should focus on developing ways to accelerate the integration of viable transplanted cells with the recipient's brain, prolong their survival and stimulate further differentiation, axonal growth and transplant innervation. Many important technological modifications have been proposed for this purpose:

—inhibiting inflammation that develops in the transplant by introducing protocols for cultivating and differentiating IPSCs without the use of xenogeneic feeder cells and media containing animal-derived components [33];

—using special enzymes to inhibit proteoglycans, which are part of the extracellular matrix and suppress axonal growth [31];

—activating IPSCs differentiation into dopaminergic neurons and their survival, by using docosahexaenoic acid and other small molecules [19] or peptide compounds [44];

—enriching the precursors of dopaminergic neurons by targeted sorting and selection of cells with the required phenotype [23];

—virus-free production of IPSCs by direct delivery of reprogramming proteins to somatic cells [35].

The above results of experimental and clinical foetal midbrain transplantation support the possibility of long-term survival, growth and integration of dopaminergic neurons in the recipient's brain, so they can

serve as a good standard for assessing the quality of dopaminergic neurons differentiated from IPSCs. Thus, the number of surviving human foetal dopaminergic neurons implanted into the rat brain ranged from several hundred to about 4000 per transplant, and 500–700 living functional cells were enough to correct drug-induced rotational behaviour. In contrast, although 5000 to 29000 implanted dopaminergic cells obtained from IPSCs survived, at least several thousand were required to completely correct the motor skills [52]. Foetal dopaminergic neurons experienced intensive neuritic growth of up to 6 mm and reinnervated the whole striatum [15, 20]. Neuritic growth in dopaminergic neurons differentiated from IPSCs varied from one case to another, but generally remained limited to within the transplant boundaries or extended beyond it into the striatum by no more than 2–3 mm, reinnervating a maximum of 10%, despite the large number of surviving neurons [23]. Thus, the differentiation protocols in use until recently, most likely do not ensure the creation of a completely specific population of type A9 foetal dopaminergic neurons, which possess internal properties that enable them to innervate the striatum.

Several review articles [38, 39] have formulated the main problems that need to be solved to successfully use IPSCs in patients with PD in clinical practice.

Firstly, dopaminergic neurons differentiated from IPSCs should have a high therapeutic potential when transplanted into the brain of experimental animals with PD models, and, above all, compensate for the lost functions, which can be achieved through active axonal growth from the transplant and the release of dopamine from axon terminals. A quantitative assessment of axonal growth ability will determine the optimal number of cells for transplantation and the number of transplants needed for each recipient.

Secondly, the transplantation should be safe. The risk of dyskinesia must be minimized and transplant tumorigenicity completely excluded, so it is important to determine the identity of all its cell types and eliminate oncogenic cells by sorting.

Thirdly, it is important to select the most 'appropriate' patients for the first clinical use of dopaminergic neurons derived from IPSCs. The candidate for such neurotransplantation should have a high chance of therapeutic success, specifically, have a clinically evident but not late stage of the disease, when the dopaminergic innervation deficiency is limited to the caudate/putamen and does not extend to the forebrain.

To clinically use IPSCs in cell therapy, it is important to avoid immunological problems such as graft-versus-host response, which is possible with this technology, since personalized IPSCs lines can be obtained for each patient. Although the brain is considered an immune-privileged zone, it has been shown that there is a difference between transplantation of autologous and allogeneic cells that do not match the recipient's main histocompatibility complex [42]. Nevertheless, while autologous cell therapy is ideal in theory, reprogramming the original cells into IPSCs and further differentiating them for each patient is very expensive and time-consuming. As an alternative, researchers at Kyoto University have launched a Cell Stock Project, which provides a bank of different IPSC lines from HLA-homozygous donors. It was estimated that 50 lines of HLA-homozygous IPSCs will cover 73% of the Japanese population when typing and accounting for the three main loci (HLA-A, HLA-B, and HLA-DR) [45]. It is worth noting that other 'minor' HLA specifics or innate immune system cells, such as macrophages and NK-cells, may also contribute to the immune response. In general, researchers should consider the advantages and disadvantages of autologous and HLA-matched allogeneic transplantation in each case, before determining which cell types to transplant.

The greatest achievement in neurotransplantation in PD was the work done by Japanese researchers, published in 2017 [34]. The authors showed that dopaminergic neuronal precursors obtained from human IPSCs, when transplanted into the putamen of macaques with a toxic MPTP model of PD, can survive for a long time in the recipients' brains, become mature neurons, and have a clear therapeutic effect during at least 2 years of follow-up. According to histological analysis, implanted dopaminergic neurons formed a dense neuritic network in the host's striatum, and this effect was the same for cells obtained from healthy donors and from patients with PD. Implanted cells that underwent sorting using the CORIN marker (serine protease expressed in the floor plate during embryonic brain development) did not form any tumours in the host brain throughout the follow-up period. The article presents convincing MRI and PET evidence of the survival, expansion and dopaminergic activity of the transplant, as well as a lack of an immune response, with the use a standard immunosuppression protocol [34]. These breakthrough findings, obtained through the long-term analysis of neurotransplantation results in a PD model in primates, open the door to the clinical use of neuronal dopaminergic IPSC derivatives in patients with PD.

Clinical trials of neurotransplantation should comply with strict standards and recommendations, set out by the International Society for Stem Cell Research [36]. In our country, an important regulatory step was the adoption of Law no. 180-FZ On Biomedical Cell Products in 2016. Progress in this field is greatly facilitated by the establishment of GForce-PD (www.gforce-pd.com), an international consortium of specialists, which is focused on improving neurotransplantation technology and rapidly transferring the results of experiments to clinical practice. As part of this program, the effectiveness of three sources of

dopaminergic cellular material—foetal mesencephalic cells (European Union and UK), neuronal ESC derivatives (USA and UK) and neuronal IPSC derivatives (Japan and USA) will be compared in patients with PD. If foetal cell transplantation will be, in a sense, a 'repeat of the past' (at a higher technological level, of course), it will truly be a revolutionary step for stem cell-derived neurons (ESCs, IPSCs).

This review has focused on PD, since this disease is a driver in developing theoretical and applied fundamentals of cell therapy [50]. However, successful neurotransplantation is relevant for other neurodegenerative diseases, stroke, spinal injury and others [5, 43, 49]. It is obvious that the powerful impetus in neurology caused by the rapid development of stem cell technologies will largely determine the face of this clinical specialty in the next decade.

While this paper was going to print, leading news websites reported on November 9, 2018 that experts from the University of Kyoto had performed the first transplant of dopaminergic neurons obtained from autologous IPSCs in a patient with Parkinson's disease.

Thus, to answer the question in the article title, we can confidently say that the time for neurotransplantation has come!

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests.The author declares there is no conflict of interest.

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