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POTENTIAL OF STEM CELL THERAPY IN TREATMENT OF PARKINSON'S DISEASE

Suchita S. Chaudhari*, Sharayu U. Rajput, Pranita V. Patil and Jyoti Kedar

Department of Biotechnology, H.P.T. Arts & R.Y.K. Science College, Nashik – 422005.

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***Corresponding Author**
Suchita S. Chaudhari
Department of Biotechnology, H.P.T. Arts & R.Y.K. Science College, Nashik – 422005.

ABSTRACT

Parkinson's disease is slow developing dopaminergic disorders which shows asymmetric or unilateral motor symptoms. Dopaminergic therapies are widely used in the treatment of Parkinson's disease. In these article we have studied various human embryonic stem cell method. Embryonic stem cell extracted from mouse blastocyst mainly were used. various types of stem cells are being used's. We have also started methods and characteristics of the embryonic stem cell. Human induced pluripotent cells were shown promising activity against parkinson's disease in various clinical trials. The embryonic stem cells therapy has various problem including the monitoring of therapy and requiring the clinical permission for the safe. Totipotency which is one of the major properties of the embryonic stem cell can be prove as the evolutionary for the treatments of various disease like AIDS, cancer, Parkinson's disease and other chronic disorders. Animal trials have been performed by using embryonic stem cells, and has shown promising results. Clinical trials are being doing right now and also showing much promising results. In future embryonic stem cell therapy right prove as the promising and safer way to procure the deadly chronic Parkinson's disease like conditions.

KEYWORDS: Parkinson's disease, Embryonic Stem Cell, Human Embryonic Stem Cell Mesenchymal cells, Neural stem cell.

INTRODUCTION

Parkinson's disease starts with asymmetric or unilateral motor symptoms.

Due to combination of mild bradykinesia, rigidity, and tremor. Some patients may show generalized bradykinesia appears, which additionally accompined with facial masking, reduced voice volume, and slowing of the activities of daily livings.[1]

Sleep disorders are also common in the Parkinson's disease. parkinson's disease include sleep related problems like insomnia, restlessnes. Rapid eye movement, sleep disorders, sleep apnea, parasomnias, excessive daytime, sleepiness and sleep attacks.[2]

Various treatments are available to treat the Parkinson's disease. Dopaminergic therapics such as levodopa treatment are very much popular for the treatments. Dopaminergic therapy shows less side effects which are not much more serious. Through it is use full and slow down the progression of disease so it needs to be develop more promising therapies for the parkinson's disease.[3]

Parkinson's is due to neuro-degenerations of dopaminergic neurons. Stem cells therapy may be acts as the source for the dopaminergic neurons to cure Parkinson's disease starts.

Dopaminergic cell lines has prepared for the testing of model of the parkinson's. which is called as the primate model of Parkinson's disease . Replacing damaged cells might appear easy but it is much more challenging tasks for the physicians to do this stem cell has it own disadvantages. which will be discussed later on it this paper.[4]

In mice it has shown promising results to cure Parkinson's disease with the help of reprogrammed pluripotent the stem cells. Reprogrammed cells are well known as induced pluripotent cells. which used to combat the Parkinson's disease. This also used to treat anemia (sickle cells) anemia in the mice i.e animal studies.[5]

Human embryonic stem Cells

ES cells are derived from the development stages of an embryo. They are divided EC cells. ES cells are come from the inner mass of a blastocyst. The first ES cells lines were extracted from mouse blastocyst in 1981, and later human ES cells lines were generated. For clinical application, under chemically defined condition without any contact with non-human proteins. ES cells able to proliferate with no limits of self-renewable and giving rise to cells that are derived from all the characteristics of true stem cells. EC cells can give rise to tumors, termed teratocarcinomas. Same as ES and EG cells, EC cells can be expand continuously and differentiated under certain condition to give rise to the three type of germ

layer cells.[6] Glial reaction and inflammation process may participate in a cascade of neuronal degeneration in PD.[7]

Stem cells are undifferentiated unspecialized cells. Stem cells are classified as follows: Totipotent, Pluripotent and Multipotent cells. Totipotent: up to the 16-cell stage early embryo all the cells are totipotent. They can give rise to every cell type within the body and placenta. Pluripotent or ES cells: are capable to produce all type of cell within the body excluding placenta, and are the cell isolated from inner cell mass of the blastocyst[8].After mouse ES cells transplantation into the knee joint to assess their ability to form cartilage , 8 weeks later it have been detected that knees is destroyed by teratoma formation. This indicate that ES cells are pluripotent.[6] Multipotent cells: are derived from the foetal and adult tissue. Mostly they are defined by the organ in which they resides. Same as ES cells they have ability to self-renew but they are more restricted.[8] The "default pathway" of differentiation of ES cells, so it has been observed ESC in cultured easily differentiated into NPCs. When exposed to inducing signals like FGF.[9]

Characteristics

High differentiation capacity of ES cells makes it suitable for cell replacement therapy. ES cells have the ability to differentiate into a neural lineage, including DAergic neurons. Thus, this type of stem cells used as a donor tissue for transplantation of PD patients. As it is mentioned earlier they have high telomerase activity, which prevents the shortening of the telomerase at the ends of chromosome each mitosis, due to this ES cells undergo unlimited division. There are several cells that are considered as a donor cells for PD: The first source of donor tissue for PD is embryonic/ fetal ventral mesencephalon (VM). Stem cell are broadly used in regenerative medicine. The second source of donor tissue for PD are the neural stem cells (NSC), which are derived from embryonic/fetal or adult brains. This type of stem cells unable to differentiating along neural cell lineage, i.e into neurons, astrocytes or oligodendroncytes. The third source of donor cell for PD is embryonic stem cell (ESC) derived from inner mass of the blastocyst.[10] As they show high tolerance activity means they are not so sensitive to senescence that is they are suitable for long-term culture. Also most commonly used sometic stem cells are Neural stem cells (NSC) and bone marrow stem cell(BMC) for Neurodegenerative disease.[6]

NSC: Neural tissue that give rise to multipotent cell type which are committee to neural lineage are termed as NSC. Organization of such type of cells is developing nervous system,

mid-brain and forebrain. In human brain, NSC's are in abundant in sub-ventricular zone and sub-granular zone of hippocampus dentate gyrus.[10,6] The differentiation properties of neuronal progenitors are depends upon the brain region from which they have been isolated that means they have regional specification. As Neural stem cell/ progenitor cell can excite to grow with the help of motigens only until they approaches their natural senescence limit in culture, the application of NS in banking and transplantation may not be optional. Another way is to immortalize progenitor cell and neural stem cell by halting cell at specific stage of development and preventing their terminal differentiation [6].NSC obtain from VM(ventral mid-brain) produced more DA neuron than NSC from other parts of the central nervous system under optimal culture conditions.[10]

hESC Cells: At first, ESC lines was established from the inner cell mass of a mouse blastocyst in 1981.[10] According to the latest report it has been demonstrated that effective neuronal differentiation of human ES cells can take place when the cells are culture under serum-free condition in the presence of 50% line HepG2.To prevent rejection of grafted mouse ES cells rat hosts accepted immunosuppression by s.c. injection of cyctopurine.[11] Neurons formation occur on differentiation of expanded neural progenitor-derived human ES cells. Human EC cells can give rise to neurospheres when cultured under differentiation medium containing retinoic acid. Early embryonic cells, all ES cells can be expanded in culture while retaining the functional attributes of pluripotent which makes them most suitable as a potential source of donor tissue for transplantation in PD. To increase ES differentiation potential genetic modification can be made by transgenesis or vector targeting.[6] With various differentiation protocol, it is difficult and complicated to generate high yields of dopaminergic neurons from hESC's.[12] Genetic manipulation of ESCs done by DA inducing transcription factor like Nurrl and Lmxla.[13] Two important protocol are mostly used to generate DA neurons from ESCs. In first protocol neural progenitor are formed by generation of embryoid bodies further more this are subjected to various growth factors in order to stimulate their differentiation into DA neurons. And the second type of protocol contains co-culture of ESCs on special forms of feeders. Soluble factor that induces formation of DA neuron are specific midbrain factor such as SHH, FGF8 and Ascorbic acid. According to recent studies it is stated that human fetal midbrain astrocystes immortalized by overexpression of telomerase facilitate the development of DA neurons from human ESCs. All this culture techniques are widely used due to its simple and fast method.[14] (ESC) have the highest proliferation and differentiation rates, but tumor formation may constitute a real

safety risk. Neural stem cells (NSC) undergo neural differentiation but less commonly to dopamine (DA) neurons. The advantage of NSC is its lower risk of tumor information. Other stem cells such as bone marrow stem cells have the advantage of the possibility of autologous grafting. Whether transdifferentiation can occur across the border of the germ layers remains controversial (? unknown, − none, ± poor, + some, ++ readily observable, +++ extensive).[10]

Human induced pluripotent cells in parkinson's disease

hiPSCs/hESCs have been entail to be very useful in parkinson's disease, cell replacement therapy, disease modeling and drug screening. Research have been made to amend application of hiPSCs/hESCs. Subsequently intens distribution on clinical trial. Design of cell replacement therapy, including patient selection, graft tissue preparation and processing and optimization of surgical procedure, a new clinical trial has been established and is presently ongoing cross-continentally in multi-research. Succcess of this trial will have a major impact on neural transplantation with fetal DA tissue and also with hESC and hiPSC derived DA neurons in future.

hiPSCs give contribution to study Neurodegenerative diseases and may in the future, be use for cell therapy as well. Due to lack of effective protocol of hiPSC differentiation and transplantation its application is limited. Despite of improvement in protocol still many problems exist. Due to lack of efficiency of generating a large quantity and well defined population of DA from iPSCs, it potential is low to treat PD.[14]

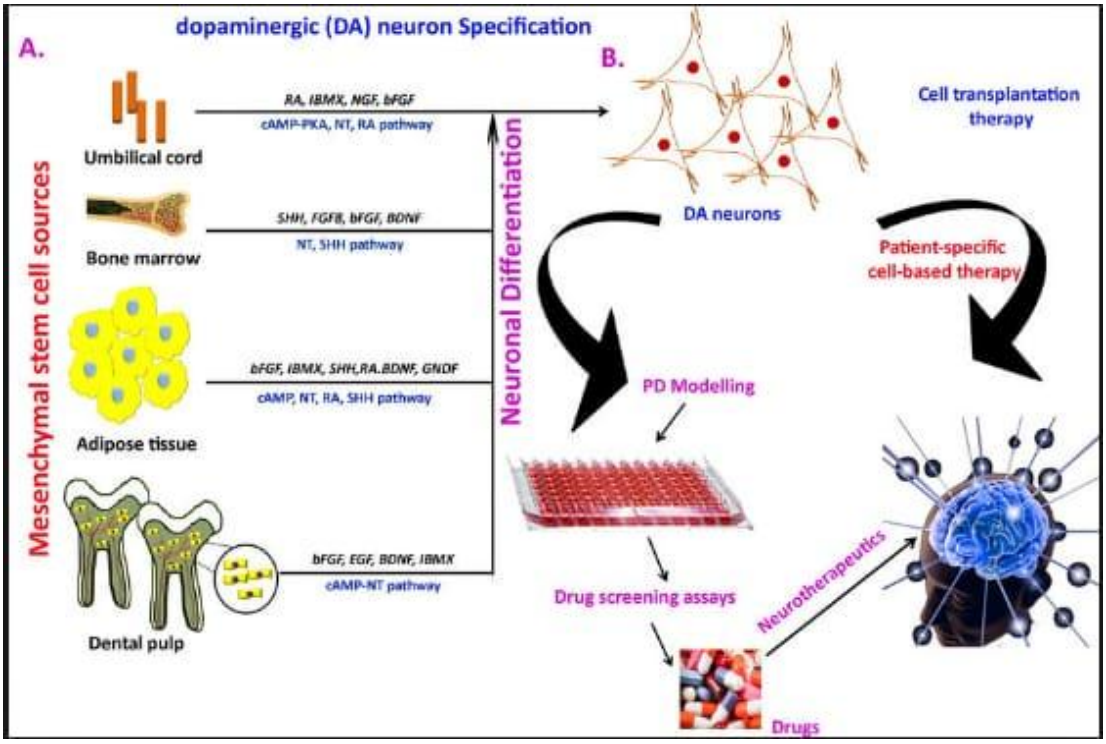

Fig. 1: Transplantation in PD patients.

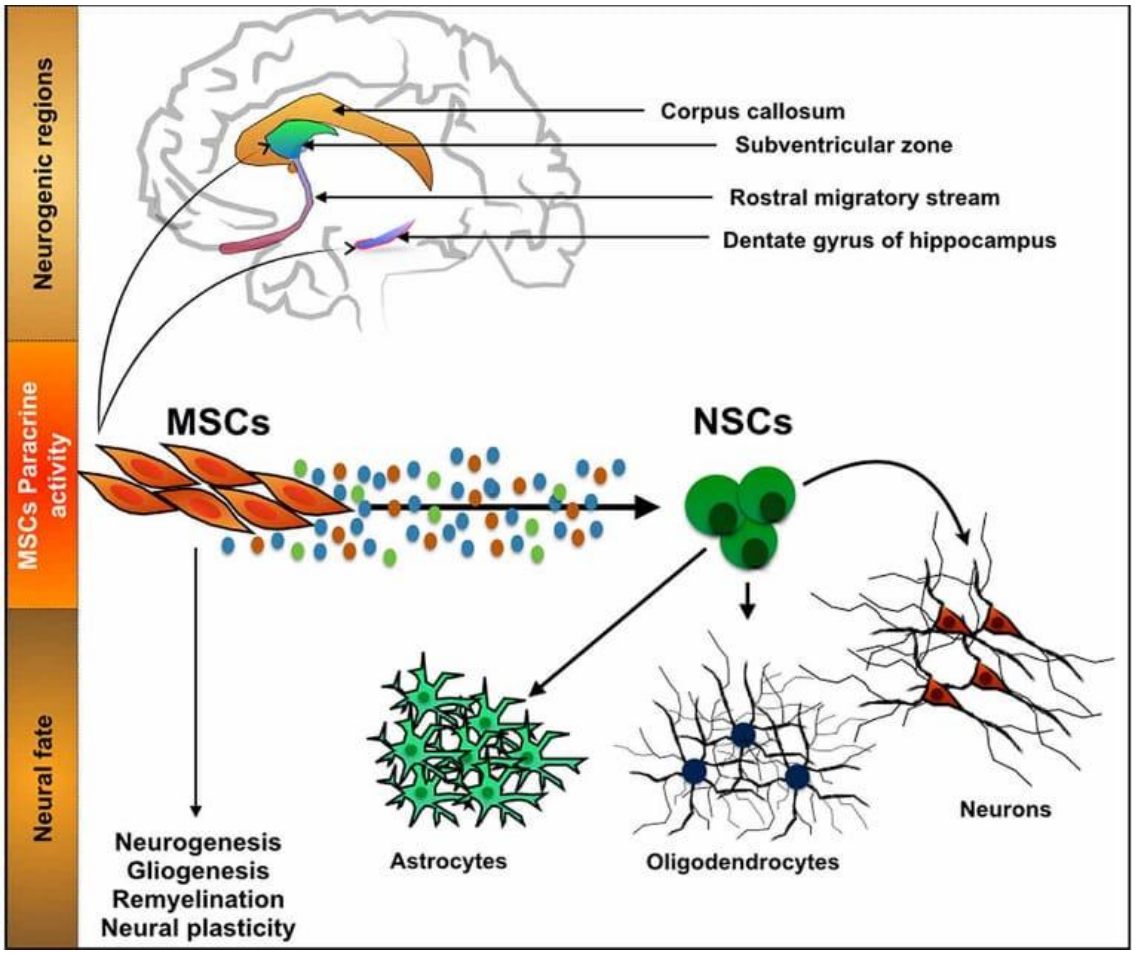

Fig. 2: Respond of brain part to PD, (Transplantation).

Future scopes of pd

From our above points and explanation we have summarised the further applications and uses of stem cell therapy. We already have conducted safe animal trials and the future in human treatment is yet to be explored. From the previously conducted clinical trials, we have reached an outcome that, in future we'll be in position to start incorporation of stem cells in the human body.[15]

Problems involved

Practising and mastering any scientific advancement is very difficult and mostly time consuming process due to its need of very careful and critical monitoring before it's tested on humans. So similarly there are many difficulties associated with the stem cell therapy. The foremost is the full understanding of this concept of cell therapy. It's effect is yet been studied on animal models and is still in process so if it's still incomplete on animals its testing on humans is quite far to think about and has a long way to go.[16]

If the neurons are grafted in a patient the problem in long run is that the patient's own dopaminergic neurons. Only some patients are able to return to normal life with production of their own dopamine in body, but the present results are not optimal to be tested on ongoing patients with Parkinson's disease. Immunosuppression is required to avoid the graft rejection by the receiver's body. The new cells needed to be developed that are resistant to the problems faced in grafting treatment.[17]

Ethical issues

The stem cell therapy is the most promising approach for the treatment of Parkinson's disease. The past few years has been dramatic in the development of stem cell research. Many safety issues and regulatory conditions are needed to be overcome in coming 5-10 years before full fetched practice of the stem cell therapy in regular practice. Over the past few years the biotech company Geron corporation has worked towards convincing about the safety of heSC-derived oligodendrocytes (GRNOPC1) and their suitability for transplantation therapy to the food and drug administration. The risk of tumour formation always remains during any transplantation therapy.[18]

The prominent goal of ESC-Transplantation is to make behavioural improvement in the patient. Presently there are some problems with ESC-Transplantation, first as we saw is the major possibility of tumour formation in the patient's body, second is the ethical issues with

use of ESC cells for research and clinical purposes, and also the rejection of transplanted cells by the host body is also an major issue. The treatments for PD in the coming years can be made feasible only if we're able to overcome the immunological barriers and are able to develop more advances in this field using our knowledge of embryonic stem cells.[19]

The "therapeutic cloning" is similar to "reproductive cloning" hence it is necessary to clarify the purpose of establishment of new human embryonic cells lines. According to catholic believes destruction of preimplanted blastocyst is considered as abortion and hence any laboratory experiment on embryonic cells is banned in many countries.[20]

Clinical trials

In the recent years our ability to produce the transplantable ESC has improved and needs to be improved more. The complete safe trials has not yet been conducted on animal models, and for it there are few advancements we advancements we need to work on 1) The risk involved in the transplantations needs to be reduced, 2) To search for markers and use them to identify transplantable cells from non-transplantable ones, 3) To reduce the inflammatory response from the host body i.e. immunosuppression 4) Improve the imaging methods to monitor the grafts precisely 5) There is need to work on animal models to get perfect results of the transplantations.

From the previous clinical trials conducted we can be hopeful of the fact that more research work in this field will lead us to very positive results and we'll be able to treat patients with Parkinson's disease with stem cells in future.[21]

Genetic instability is an another issue, karyotypic changes in several humans is common and changes commonly occur in chromosome number 12 and 17, we're not completely sure about it but this can result in chromosomal abnormalities and may increase the risk of tumour formation in the host body. Also it is being proposed that non-human material could also be used for trials.[22]

Concluding remark

The stem cells have very special characteristic feature of toti potency i.e. differentiating into any expected cell type and this property can prove as an evolution in the treatments of different diseases, and even fatal disorders like Aids, Cancer, Parkinson's disease, etc. The growth is an continuous process in human body but the cells have the property to differentiate

into only specific tissue and most cells cant regenerate themselves but the plant cells have this property and the whole plant can be generated from any provided part of plant, and this property in humans only resides in liver cells, whole liver can be regenerated from even a small portion of cells. Preserving the stem cells at the time of birth can prove as a boon for a life, and awareness is being spreaded regarding the same, and special stem cell banks are being maintained for this purpose.

REFERENCES

1. Tarsy, D. Treatment of Parkinson Disease. JAMA, 2012; 307(21): 2305. https://doi.org/10.1001/jama.2012.4829.
2. Zesiewicz, T. Sleep disorders in Parkinson’s disease. Neuropsychiatric Disease and Treatment, 2009; 535. https://doi.org/10.2147/ndt.s4578.
3. Olanow, C., & Schapira, A. Therapeutic prospects for Parkinson disease. Annals of Neurology, 2013; 74(3): 337-347. https://doi.org/10.1002/ana.24011.
4. Langston, J. The promise of stem cells in Parkinson disease. Journal of Clinical Investigation, 2005; 115(1): 23-25. https://doi.org/10.1172/jci200524012.
5. Borthwick, L. Stem cells improve Parkinson's disease symptoms. Nature Reports Stem Cells, 2008. https://doi.org/10.1038/stemcells.2008.63.
6. Barker, R., & Farrell. Stem cells and regenerative therapies for Parkinson’s disease. Degenerative Neurological and Neuromuscular Disease, 2012; 79. https://doi.org/10.2147 /dnnd.s16087.
7. Lee, P ., & Park, H. Bone Marrow-Derived Mesenchymal Stem Cell Therapy as a Candidate Disease-Modifying Strategy in Parkinson's Disease and Multiple System Atrophy. Journal of Clinical Neurology, 2009; 5(1): 1. https://doi.org/10.3988/jcn.2009.5.1.1.
8. Parish, C., & Arenas, E. Stem-Cell-Based Strategies for the Treatment of Parkinson’s Disease. Neurodegenerative Diseases, 2007; 4(4): 339-347. https://doi.org/10.1159/000101892.
9. Vidaltamayo, R., Bargas, J., Covarrubias, L., Hernández, A., Galarraga, E., Gutiérrez-Ospina, G., & Drucker-Colin, R. Stem Cell Therapy for Parkinson’s Disease: A Road Map for a Successful Future. Stem Cells and Development, 2010; 19(3): 311-320. https://doi.org/10.1089/scd .2009.020.

10. Morizane, A., Li, J., & Brundin, P. From bench to bed: the potential of stem cells for the treatment of Parkinson's disease. Cell and Tissue Research, 2007; 331(1): 323-336. https://doi.org/10.1007/s00441-007-0541-0.
11. Bjorklund, L., Sanchez-Pernaute, R., Chung, S., Andersson, T., Chen, I., & McNaught, K. et al. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proceedings of The National Academy of Sciences, 2002; 99(4): 2344-2349. https://doi.org/10.1073/pnas.022438099.
12. Lindvall, O., Brundin, P ., Widner, H., Rehncrona, S., Gustavii, B., & Frackowiak, R. et al. Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science, 1990; 247(4942): 574-577. https://doi.org/10.1126/science.2105529.
13. Ambasudhan, R., Dolatabadi, N., Nutter, A., Masliah, E., Mckercher, S., & Lipton, S. Potential for cell therapy in Parkinson's disease using genetically programmed human, embryonic stem cell-derived neural progenitor cells. Journal of Comparative Neurology, 2014; 522(12): 2845-2856. https://doi.org/10.1002/cne.23617.
14. Li, W., Chen, S., & Li, J. Human induced pluripotent stem cells in Parkinson's disease: A novel cell source of cell therapy and disease modeling. Progress In Neurobiology, 2015; 134: 161-177. https://doi.org/10.1016/j.pneurobio.2015.09.009.
15. Arenas, E. Towards stem cell replacement therapies for Parkinson's disease. Biochemical and Biophysical Research Communications, 2010; 396(1): 152-156. https://doi.org/10.1016/j.bbrc.2010.04.037.
16. Zakrzewski, W., Dobrzyński, M., Szymonowicz, M. and Rybak, Z., Stem cells: past, present, and future. Stem Cell Research & Therapy, 2019; 10(1).
17. Lindvall, O., Kokaia, Z., & Martinez-Serrano, A. Stem cell therapy for human neurodegenerative disorders–how to make it work. Nature Medicine, 2004; 10(S7): S42-S50. https://doi.org/10.1038/nm1064.
18. Brundin, P., Barker, R., & Parmar, M. Neural grafting in Parkinson's disease. Progress In Brain Research, 2010; 265-294. https://doi.org/10.1016/s0079-6123 (10)84014-2.
19. Takahashi, J. Stem cell therapy for Parkinson's disease. Expert Review of Neurotherapeutics, 2007; 7(6): 667-675. https://doi.org/10.1586/14737175.7.6.667.
20. Fukuda, H., & Takahashi, J. Embryonic stem cells as a cell source for treating Parkinson's disease. Expert Opinion On Biological Therapy, 2005; 5(10): 1273-1280. https://doi.org/10.1517/14712598.5.10.1273.

21. Arenas, E. Towards stem cell replacement therapies for Parkinson's disease. Biochemical and Biophysical Research Communications, 2010; 396(1): 152-156. https://doi.org/10.1016/j.bbrc.2010.04.037.
22. Morizane, A., & Takahashi, J. Embryonic Stem Cell Transplantation for the Treatment of Parkinson's Disease. Perspectives of Stem Cells, 2009; 245-254. https://doi.org/10.1007/978-90 -481-3375-8_15.
23. Isacson, O., Costantini, L., Schumacher, J., Cicchetti, F., Chung, S., & Kim, K. Cell implantation therapies for Parkinson's disease using neural stem, transgenic or xenogeneic donor cells. Parkinsonism & Related Disorders, 2001; 7(3): 205-212. https://doi.org/10.1016/s1353 -8020(00)00059.