Stem Cell Therapy as a Potential Treatment for Motor Symptoms in Parkinson's Disease

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Parkinson's disease is a neurodegenerative disease stimulated by the lack of DA neurons in the midbrain. Onset usually occurs around and after 60 years old, in which patients experience a variety of motor deficiencies and non-motor symptoms. This review focuses on the use of three stem-cell derived products - embryonic stem cells, mesenchymal stem cells, and human induced pluripotent stem cells - to treat motor symptoms of Parkinson's disease. A streamlined production, differentiation, and proven regenerative properties highlight stem cells as a candidate to prevent neurodegeneration. Along with the obvious benefits of stem cell treatments, there exist many physical and ethical drawbacks with their production, transplantation, and overall use. Regardless, stem cells stand as the future of Parkinson's disease treatments and one that can be exploited even further.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease primarily caused by an obstruction to the midbrain dopaminergic pathway. PD is also characterized by a buildup of alpha-synuclein in the basal ganglia. The formation of lewy bodies is caused by misfolding, either from environmental factors or genetic predisposition. The primary symptom is motor dysfunction, including hand tremors, gait abnormalities, and muscle rigidity. Non-motor symptoms of PD also include anxiety, depression, and hypersomnia. Most symptoms of PD are attributed towards the aggregation of alpha-synuclein to form Lewy bodies, while the exact cause is not known. Aging has also been shown to increase symptoms and the severity of PD. Although research is ongoing, no cure or long-term treatment has been found to treat either motor or nonmotor symptoms of PD. Therapies such as Deep Brain Stimulation, L-dopa, or enzyme reuptake have only offered temporary symptomatic relief.

Although stem cells were discovered in the early twentieth century, their potential use in medicine as a neurodegenerative disease treatment has only been investigated in the last few decades, especially through the recent BRT-DA01 trial. The diversified differentiation of stem cells has allowed scientists to use them in replacing depleted tissues, and in the case of neurological problems, brain areas or cell types most heavily affected by neurodegeneration. Several sources of stem cell derivation and methods for injection and differentiation have been investigated in the last few years, especially for cardiac and brain tissue replacement (Figure 1). Embryonic stem cells (ESCs) were established as the first form of reproducible stem cells. Matched with ethical concerns, these were replaced in research with more regulated forms, as discussed further in the paper.

Embryonic Stem Cells

The use of fetal tissue as a source for replaceable neurons is one of the two major sources, along with stem cells. Fetal tissue-derived neurons were developed as a major source for regenerative cells in the mid-1980s, but significant breakthroughs only came in the last few decades with active transplantation[1]. Fetal ventral mesencephalon (fetal VM) is defined as a section of the ventral midbrain, particularly the mesencephalic region. In recent years, it has emerged as a source of Parkinsonian treatment. In recent years, the derivation of fetal VM has been popularized early in the gestational period, especially in failed embryos to avoid ethical concerns[2]. Fetal VM cells have been proven to easily differentiate into more viable embryonic stem cells (ESCs) for further neural differentiation[3]. ESCs are commonly used for advanced differentiation of neural progenitor cells.

Fetal VM is often referred to as a viable source of stem cells for neurodegenerative diseases due to high stem cell viability and robust differentiation. Several studies have shown the ability of stem cells to differentiate into neurons, astrocytes, and oligodendrocytes[4,5]. Using common markers of neurogenesis to label various items, researchers determined the increase in markers when performing an in vivo graft. This study consisted of both hESCs and Fetal VM cells to contrast the varied distribution of cells into greater neural networks. Single cell RNA-sequencing (scRNA-seq) results showed that several common markers of advanced neurogenesis, such as LMX1A, are commonly found in both groups. In addition, there was an increase in expressed genes for all three major neural sectors after 6 months of anal-

ysis in fetal VM cells, while only astrocytes and neurons were expressed in hESCs. Researchers concluded that statistical differences in the study are due to the structural incapabilities of hESCs to differentiate into extensively growing cells compared to the relative freedom of fetal cells. Researchers reported an increase in dopaminergic (DA) neurons in the graft solution at 6 months post-graft which they viewed as beneficial for treatment of PD[6].

However, ethical concerns plague the question of Fetal VM use in neurodegenerative disease treatment[7,8]. The same clinical trial reported the expected inability of legal and accessible fetal VM sources as an additional cost for its future commercial use[6]. Additional fetal VM clinical trials face similar issues, including TRANSEURO[9–11]. TRANSEURO discussed the need to find a wide variety of viable sources for fetal VM donors[9]. This was widely contrasted with the increased availability of mesenchymal stem cells (MSCs) among widespread laboratories in Europe[12]. Even though this was not taken into the general results, other sources have included this as an important diminutive against commercial Fetal VM use[9,10]. Embryonic stem cells face the same ethical problems against their widespread use.

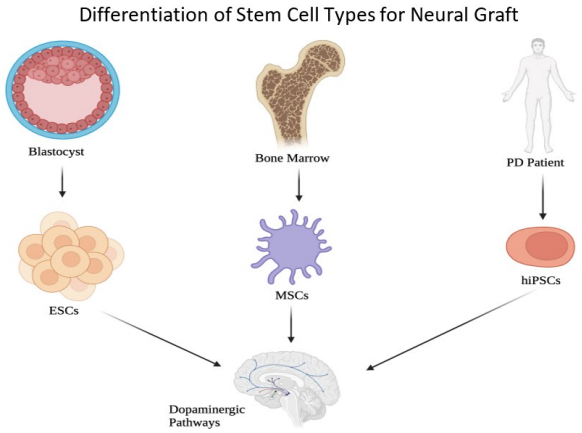

Fig. 1 Figure 1. Differentiation of Stem Cells for Neural Graft.

Figure 1 shows the common derivation sites of regenerative embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), and human induced pluripotent stem cells (hiPSCs). From extraction, each undergoes differentiation and development until able for transplant. (from BioRender)

Mesenchymal Stem Cells

Another pioneered field in stem cell transplantation for PD and other neurodegenerative diseases is the use of MSCs[13]. Mesenchymal stem cells were discovered in the 1960s as derived from bone marrow and with other hematopoietic and regenerative properties[14]. Previously, MSCs were used as progenitors for tissue engineering and regeneration in other parts of the body. Experiments involved in the use of MSCs for other parts of the body referenced uses in angiogenesis, osteogenesis, as well as muscle reconstruction[5]. Before use in PD and other neurodegenerative diseases, MSCs were recorded as a success in treating other tissue damage disease, especially in later timepoints of tissue recovery[15].

MSCs were first instrumented in neurodegenerative disease treatment due to numerous advantages such a lack of tumorigenesis and varied sources to derive the stem cells[16,17]. Although both treatments are relatively recent, the advent of MSCs in treating PD was compared to the gold standard of stem cell treatment in the 2000s: embryonic, specifically fetal, stem cells (ESCs). In comparison to MSCs, ESCs had a higher rate of tumorigenesis, even in human trials. Clinical trials show that differentiation in in vivo grafts of neural stem cells (NSCs) and fetal ESCs are correlated to signs of tumorigenesis in the regeneration of glial cells and astrocytes[18]. In the 1980s, the use of fetal-derived materials in the lab, especially ESCs, were halted because of Roe vs. Wade[19]. The decision increased uncertainties among researchers and diverted attention to other stem cell sources. In addition, studies reference the inefficiency of ESCs in rapid differentiation as a factor for the early disposal of dysfunctional embryos. Although other nations are not actively affected by this issue, the United States banned the production of human ESCs (hESCs)[9]. Manufacturers and production industry in the United States has therefore either diverted to less efficient usage of ESCs or has turned to MSCs and other types of stem cells as less controversial options.

Exosomes of Mesenchymal Stem Cells as a Parkinson's Disease Treatment

An exosome is an extracellular vesicle released by the host cell. They are released for a variety of reasons in different cells, including cell-to-cell communication and angiogenesis. In neural cells, they are almost always primarily used for short-distance communication between non-conjoined neurons through the transfer of macromolecules and receptors[20]. Exosomes have been derived from MSCs and exhibit specific properties that make them more efficient compared to those derived from other stem cell types. MSC-derived exosomes have higher enzyme content, which enhances exosomal transport and metabolization of molecules[21]. MSC-derived exosomes also exhibit specific cytokines and growth factors that can regulate the immune system. Scientists have used this characteristic to identify an advantage for tissue repair from MSC-derived exosomes[22]. MiRNAs have also been discovered in MSC-derived exosomes, which play a part in coding for tissue growth, but also immunosup-

pression[23]. Studies directly correlate MiRNA abundance as a potential reason for the low immunogenicity of MSC-regulated neurodegenerative disease treatments[17].

Several treatments regarding MSC-derived exosomes focus on the production and aggregation of alpha-synuclein (aSN) in the ventral midbrain[21]. Prior studies show that the aggregation of aSN blocks important neural networks in the basal ganglia and can lead to Parkinsonian symptoms (24). Many prior treatments for the treatment of PD treat outer symptoms and have variable effects on PD individuals. While other stem cell treatments described also target the causes of the disease, treatment with MSC-derived exosomes is specifically targeted towards the root cause[24]. Most treatments currently involving MSC-derived exosomes use them as a supplement for other regenerative or palliative treatments for PD such as ESCs and L-dopa. Additionally, MSC-derived exosomes provide several advantages and manners of prevention of aSN aggregation and PD progression in patients.

Human Induced Pluripotent Stem Cells (hiPSCs) for Treatment of Parkinson's disease

The invention of pluripotent stem cells is fairly recent, with the breakthrough coming in with Yamanaka's discovery in 2007[25]. The use of four specific transcription factors, notably Oct4, Sox2, Klf4, and c-Myc, can be used to differentiate fibroblasts into induced pluripotent stem cells (iPSCs)[26]. Many recent applications for human iPSCs (hiPSCs) include cancer treatments and tissue regeneration, and iPSCs have emerged as potential treatments for neurodegenerative diseases in the last few years. (28). Although hiPSCs hold just the same amount of immune resistance as ESCs when transplanted, ethical concerns about ESCs, as mentioned before, is a major deterrent away from its common use[12]. Another advantage of iPSCs is the ability to differentiate into several different forms, rather than just specified forms from their original location. The transplantation of both MSCs and ESCs either hold restrictions in the forms of previous locations for new grafting or the lack of equipment for proper and free differentiation[27].

hiPSCs are commonly used to identify new markers for neurodegenerative disease progression. Rather than using hiPSCs for transplantation therapies, host neural stem cells (NSCs) can be differentiated into hiPSCs that can undergo genetic editing to model patient diseases like PD[28]. Studies have shown that NSCs sourced from diseased patients have a higher chance of differentiating into a representative cell type relevant to a disease[29,30]. Scientists can use these NSC-derived iPSCs from other patients to graft iPSC-derived tissues in other patients with similar symptoms to the host[29]. These new in vitro models allow for the targeted use of specific drugs for the treatment of the strain[31]. Studies conducted with PD patient-specific hiPSC strains reported the successful treatment of neural tissue in a conjunctive L-dopa treated model[24]. Yet, other studies do not show this result and instead support the use of ESCs or MSCs to successfully treat PD[32,33]. Regardless of the efficacy of potential treatments when tested with the model, its development allows the assessment of treatment options for a variety of PD patients.

Discussion

Along with various primary motor symptoms, PD has several non-motor symptoms that have risen in importance in the last few years. These include depression, sleep disorders, and anxiety, especially in later-stage patients of PD[34]. Studies also show that some cases of depression and sleeping disorders can precede motor symptoms of PD and be recognized as a precursor in some patients. Another study also shows that non-motor symptoms such as hallucinations and cognitive impairment are linked with other neurotransmitter deficiencies other than dopamine, highlighting the importance of expanding current treatments for non-motor symptoms[35]. Stem cell therapies have arisen as a potential alternative for treatment of motor and non-motor symptoms due to their ability to differentiate to both dopaminergic and non-dopaminergic neurons. MSCs are currently being investigated as a potential stem cell source due to their ability to differentiate into a wide variety of target cells. MSC derivation needs to be further researched for other neurotransmitters such as acetylcholine in response to PD non-motor symptoms. Another important consideration of PD non-motor symptoms is the re-integration of graft cells into other neural networks. Studies involving stem cell transplantation for PD motor symptoms focus on the substantia nigra, yet several other components, such as the frontal cortex, have been found to affect signs of depression and anxiety in PD patients[36]. Studies also need to be done to test the efficacy of ESCs and hiPSCs when differentiating into other neurotransmitters for PD. A step towards this goal is the completed Stage 1 trial of bemdaneprocel (BRT-DA01) - a pluripotent stem cell product - from BlueRock Therapeutics[?]. A positive result in the upcoming stage 2 trial of the therapy 2 would reinforce the need for a commercially viable product.

Pre-existing methods of PD treatment, such as L-dopa and deep brain stimulation have been shown to be ineffective in treatment of non-motor symptoms as well as less effective than stem cell transplantation in treating motor symptoms. Studies show that overuse of L-dopa can lead to increased mental health issues due to unnecessary interference with other neural networks. Stem cell transplantation functions as a more streamlined and targeted method for the treatment of PD. With considerations of the ethical concerns of ESC use, studies must be done to improve the death rate of its production. For MSCs and hiPSCs research should be directed through a more efficient production rate with higher potential for differentiation. Scientists should

also look into more efficient grafting methods with stem cells. The current process wastes a significant part of the created batch, whereas a more efficient method will help diversify stem cell use further.

Conclusion and Perspective

Over the past decade, significant strides have been taken for the future creation of a safe and commercially viable stem cell treatment for Parkinson's disease. Embryonic stem cells, mesenchymal stem cells, and human induced pluripotent stem cells each have their own unique advantages and disadvantages yet provide an improved treatment over current therapies in all facets. Yet, there are limitations that can only be worked around through additional research in the field.

Methods

This paper was a systematic review conducted from the official PubMed database. Reviewed papers were selected mainly from the past five years on the topic. However, landmark papers that include pertinent discoveries from past that period were included. The main lens taken when viewing the papers was a comparative analysis, especially between the main types of stem cell-related treatment. Comparisons occurred between the level of treatment across time and the effectiveness of each treatment by preliminary tests. Key words such as "Parkinson's disease", "hiPSCs", "MSCs", and "ESCs" were used in combination to identify reviewable papers for the topic. Once again, landmark cases that do not already possess these keywords were included for their relevance to the topic. Once again, landmark cases that do not already possess these keywords were included for their relevance to the topic. Papers were also selected from within the last ten years. However, landmark cases prove to be another exception.

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References

1 K.-C. Sonntag, B. Song, N. Lee, J. Jung, Y. Cha, P. Leblanc, C. Neff, S. Kong, B. Carter, J. Schweitzer and K.-S. Kim, *Pluripotent stem cell-based therapy for Parkinson's disease: Current status and future prospects*, https://doi.org/10.1016/j.pneurobio.2018.04.005.

2 V. Krishnan, A. Sharma, R. Ramamurthy, R. Elayedatt and B. Ramamurthy, *Prenatal Ventriculomegaly – Diagnosis, Prognostication and Management*, https://doi.org/10.4103/0028-3886.332280.

3 H. Widmer and S. Santo, *Neurotrophic factor-based strategies to enhance survival and differentiation of neural progenitor cells toward the dopaminergic phenotype*, https://doi.org/10.4103/bc.bc_23_18.

4 C. Denman, H.-D. Tran, M.-K. Shin, J. Ryu, B. Kuhn and J. Jo, *Generation of a human embryonic stem cell reporter line, TMEM119-EGFP, for the visualisation of in vitro differentiated human microglia*.

5 G. Hardingham, R. Patani, P. Baxter, David and S. Chandran, *Human Embryonic Stem Cell-Derived Neurons as a Tool for Studying Neuroprotection and Neurodegeneration*, https://doi.org/10.1007/s12035-010-8136-2.

6 A. Kirkeby, J. Nelander, D. Hoban, N. Rogelius, H. Bjartmarz, P. Storm, A. Fiorenzano, A. Adler, S. Vale, J. Mudannayake, Y. Zhang, T. Cardoso, B. Mattsson, A. Landau, A. N. Glud, J. C. Sørensen, T. P. Lillethorup, M. Lowdell, C. Augusto and O. Bain, *Preclinical quality, safety, and efficacy of a human embryonic stem cell-derived product for the treatment of Parkinson's disease, STEM-PD*, https://doi.org/10.1016/j.stem.2023.08.014.

7 F. Tan, X. Li, Z. Wang, J. Li, K. Shahzad and J. Zheng, *Clinical applications of stem cell-derived exosomes*, https://doi.org/10.1038/s41392-023-01704-0.

8 F. Tan, X. Li, Z. Wang, J. Li, K. Shahzad and J. Zheng, *Clinical applications of stem cell-derived exosomes*, https://doi.org/10.1038/s41392-023-01704-0.

9 R. Barker, *Designing stem-cell-based dopamine cell replacement trials for Parkinson's disease*, https://doi.org/10.1038/s41591-019-0507-2.

10 T. Piroth, M.-C. Pauly, C. Schneider, A. Wittmer, S. Möllers, M. Döbrössy, C. Winkler and G. Nikkhah, *Transplantation of Human Fetal Tissue for Neurodegenerative Diseases: Validation of a New Protocol for Microbiological Analysis and Bacterial Decontamination*, https://doi.org/10.3727/096368913x666449.

11 S. Moore, N. Guzman, S. Mason, C. Williams-Gray and R. Barker, *Which Patients with Parkinson's Disease Participate in Clinical Trials? One Centre's Experiences with a New Cell Based Therapy Trial (TRANSEURO*, https://doi.org/10.3233/jpd-140432.

12 M. Krampera and K. Le Blanc, *Mesenchymal stromal cells: Putative microenvironmental modulators become cell therapy*, https://doi.org/10.1016/j.stem.2021.09.006.

13 A. Andrzejewska, S. Dabrowska, B. Lukomska and M. Janowski, *Mesenchymal Stem Cells for Neurological Disorders*.

14 Q. Shi, Z. Qian, D. Liu, J. Sun, X. Wang, H. Liu, J. Xu and X. Guo, *GMSC-Derived Exosomes Combined with a Chitosan/Silk Hydrogel Sponge Accelerates Wound Healing in a Diabetic Rat Skin Defect Model*, https://doi.org/10.3389/fphys.2017.00904.

15 J. Xu, X. Wang, J. Chen, S. Chen, Z. Li, H. Liu, Y. Bai and F. Zhi, *Embryonic stem cell-derived mesenchymal stem cells promote colon epithelial integrity and regeneration by elevating circulating IGF-1 in colitis mice*, https://doi.org/10.7150/thno.47683.

16 P. Khayambashi, J. Iyer, S. Pillai, A. Upadhyay, Y. Zhang and S. Tran, *Hydrogel Encapsulation of Mesenchymal Stem Cells and Their Derived Exosomes for Tissue Engineering*.

17 J. Xu, G. Liu, X. Wang, Y. Hu, H. Luo, L. Ye, Z. Feng, C. Li, M. Kuang, L. Zhang, Y. Zhou and X. Qi, *evaluation of acute and long-term routine toxicity testing in mice and rats*, hUC-MSCs:.

18 Q. Weng, J. Wang, J. Wang, D. He, Z. Cheng, F. Zhang, R. Verma, L. Xu, X. Dong, Y. Liao, X. He, A. Potter, L. Zhang, C. Zhao, M. Xin, Q. Zhou, B. Aronow, P. Blackshear, J. Rich and Q. He, *Single-Cell Transcriptomics Uncovers Glial Progenitor Diversity and Cell Fate Determinants during Development and Gliomagenesis*, https://doi.org/10.1016/j.stem.2019.03.006.

19 V. Volarevic, B. Markovic, M. Gazdic, A. Volarevic, N. Jovicic, N. Arsenijevic, L. Armstrong, V. Djonov, M. Lako and M. Stojkovic, *Ethical and Safety Issues of Stem Cell-Based Therapy*, https://doi.org/10.7150/ijms.21666.

20 M. Hade, C. Suire and Z. Suo, *Mesenchymal Stem Cell-Derived Exosomes: Applications in Regenerative Medicine*, https://doi.org/10.3390/cells10081959.

21 K. Sun, X. Jing, J. Guo, X. Yao and F. Guo, *Mitophagy in degenerative joint diseases*, https://doi.org/10.1080/15548627.2020.1822097.

22 M. Chu, H. Wang, L. Bian, J. Huang, D. Wu, R. Zhang, F. Fei, Y. Chen and J. Xia, *Nebulization Therapy with Umbilical Cord Mesenchymal Stem Cell-Derived Exosomes for COVID-19 Pneumonia*, https://doi.org/10.1007/s12015-022-10398-w.

23 V. Sengupta, S. Sengupta, A. Lazo, P. Woods, A. Nolan and N. Bremer, *Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19*, https://doi.org/10.1089/scd.2020.0080.

24 K. Sun, X. Jing, J. Guo, X. Yao and F. Guo, *Mitophagy in degenerative joint diseases*, https://doi.org/10.1080/15548627.2020.1822097.

25 K. Takahashi and S. Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*.

26 K. Takahashi, K. Tanabe, M. Ohnuki, M. Narita, T. Ichisaka, K. Tomoda and S. Yamanaka, *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*.

27 R. Maas, S. Lee, M. HarakaĽová, G. Christian, W. R., J. Hjortnaes, P. Doevendans, J. Linda, F. Asselbergs, J. Wu, J. P. Sluijter, S. Wu and J. Buikema, *Massive expansion and cryopreservation of functional human induced pluripotent stem cell-derived cardiomyocytes*.

28 A. Min Seong Kim, S. H. K. E., B. A. Seo, H. S. Ko, Y. Oh and G. Lee, *Advanced human iPSC-based preclinical model for Parkinson's disease with optogenetic alpha-synuclein aggregation*, https://doi.org/10.1016/j.stem.2023.05.015.

29 J. Schweitzer, B. Song, T. Herrington, T.-Y. Park, N. Lee, S. Ko, J. Jeon, Y. Cha, K. Kim, Q. Li, C. Henchcliffe, M. Kaplitt, C. Neff, O. Rapalino, H. Seo, I.-H. Lee, J. Kim, T. Kim, G. Petsko and J. Ritz, *Personalized iPSC-Derived Dopamine Progenitor Cells for Parkinson's Disease*, https://doi.org/10.1056/nejmoa1915872.

30 A. Bose, G. Petsko and L. Studer, *Induced pluripotent stem cells: a tool for modeling Parkinson's disease*, https://doi.org/10.1016/j.tins.2022.05.001.

31 D. Doi, H. Magotani, T. Kikuchi, M. Ikeda, S. Hiramatsu, K. Yoshida, N. Amano, M. Nomura, M. Umekage, A. Morizane and J. Takahashi, *Pre-clinical study of induced pluripotent stem cell-derived dopaminergic progenitor cells for Parkinson's disease*, https://doi.org/10.1038/s41467-020-17165-w.

32 H. Fernandes, N. Patikas, S. Foskolou, S. Field, J.-E. Park, M. Byrne, A. Bassett and E. Metzakopian, *Single-Cell Transcriptomics of Parkinson's Disease Human In Vitro Models Reveals Dopamine Neuron-Specific Stress Responses*, https://doi.org/10.1016/j.celrep.2020.108263.

33 M. Diaz-Ortiz, Y. Seo, M. Posavi, M. Carceles Cordon, E. Clark, N. Jain, R. Charan, M. Gallagher, T. Unger, N. Amari, R. Skrinak, R. Davila-Rivera, E. Brody, N. Han, R. Zack, V. Deerlin, T. Tropea, K. Luk, E. Lee and D. Weintraub, *GPNMB confers risk for Parkinson's disease through interaction with -synuclein*, https://doi.org/10.1126/science.abk0637.

34 P. Pantcheva, S. Reyes, J. Hoover, S. Kaelber and C. Borlongan, *Treating non-motor symptoms of Parkinson's disease with transplantation of stem cells*, https://doi.org/10.1586/14737175.2015.1091727.

35 A. Bruck, *Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment*, https://doi.org/10.1136/jnnp.2003.031237.

36 W. Huang, T. Zhang, X. Li, L. Gong, Y. Zhang, C. Luan, Q. Shan, X. Gu and L. Zhao, *Intranasal Administration of Umbilical Cord Mesenchymal Stem Cell Exosomes Alleviates Parkinson's Disease*, https://doi.org/10.1016/j.neuroscience.2024.04.010.