Approved by the MHLW of Japan

Program for Stem Cell Regenerative Medicine Treatment for Parkinson's Disease

Biostar

Biostar Stem Cell Research Institute

Tokyo Shinjuku Clinic

Stem Cell Technology has been approved by Japan's Ministry of Health, Labor and Welfare as regenerative medicine treatment for Parkinson's Disease at Shinjuku Clinic in Tokyo, Japan.

- This is the first case in which a treatment for Parkinson's disease has been approved using administration of Intravenous and intrathecal route with autologous adipose-derived stem cells.
- Biostar Stem Cell Research Institute has over 20 years of clinical practice in stem cell culture technology.
- The patented technology worldwide consists of cultivating stem cells to be younger and smaller in size suitable for intravenous administration, improving the homing effect of stem cells and cancer inhibition.
- When stem cells are administered intrathecally along with intravenous administration, more stem cells can migrate to the brain lesion area and increase regenerative action, thereby increasing the treatment effect.

▲ Biostar's Stem Cell Technology (120 patent applications, 76 published papers

◀ Approved for Parkinson's disease treatment by the MHLW of Japan

The safety of autologous adipose-derived stem cells cultured using Biostar's technology was confirmed for repeated intrathecal and intravenous administration to Parkinson's disease patients.

- The safety of intrathecal administration was confirmed in 70 patients with neurodegenerative diseases, including Parkinson's disease, in Japan and China from 2009 to 2017.
- Blood tests and various data have proven that intrathecal and intravenous administration of stem cells is safe even after repeated administration of stem cells up to 25 times intrathecally in 70 patients, including Parkinson's disease patients.

Journal of Clinical Case Reports

Research Article — Open Access

Safety of Multiple Intrathecal Administrations of Cultured Human Autologous Adipose-Derived Stem Cells in the Patients with Neurological Disorders Including Parkinson's Disease

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Abstract

Although autologous adipose stem cells have much therapeutic potential for incurable diseases, safety concerns have been constantly raised for clinical use. An intrathecal injection of the stem cells to improve therapeutic efficiency in central nervous system diseases is also reluctant due to concerns of adverse reaction. To investigate the safety of multiple intrathecal administrations of autologous adipose-derived mesenchymal stem cells (hAdMSCs), adverse reactions were analyzed by questionnaire survey and blood chemistry examination in 70 patients with Parkinson's disease and other neurodegenerative diseases who received hAdMSCs multiple times in China and Japan, retrospectively. As results, multiple IT administrations of cultured autologous hAdMSCs were safe, although mild back pain at the injection site in 4 patients and headache, dizziness, fever and asleep legs in other 4 patients. Adverse reactions were disappeared completely without specific treatment within a day. There were no serious adverse reactions during the cell treatment period. No remarkable atypical clinical change was observed in the blood analysis before and after the cell administrations. This study demonstrates that multiple IT administrations of hAdMSCs are safe for clinical use.

Keywords: Autologous adipose-derived mesenchymal stem cells; Intrathecal injection; Safety

Abbreviations: AD: Alzheimer's Disease; ALT: Alanine Aminotransaminase; AST: Aminotransferase; BMSCs: Bone Marrow Stem Cells; BUN: Blood Urea Nitrogen; CNS: Central Nervous System; DMEM: Dulbecco's Modified Eagle's Medium; FBS: Fetal Bovine Serum; hAdMSCs: Human Adipose-Derived Mesenchymal Stem Cell; HbA1c: Glycated Hemoglobin; HBsAg: Antigen of the Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; IT: Intrathecal; IV: Intravenous; ND: Neurodegenerative Diseases; PBS: Phosphate Buffered Saline; PD: Parkinson's Disease; VDRL: Venereal Disease Research Laboratory; γ-GTP: γ-Glutamyl Transpeptidase

Introduction

Parkinson's disease (PD) is a neurodegenerative disease (ND) showing the progressive abnormal motor symptoms such as rigidity, tremor, bradykinesia, akinesia and the dopaminergic neuronal loss accompanied by the formation of Lewy body that is primarily composed of aggregated α-synuclein in the brain [1]. Long-term loss of dopaminergic neurons in the nigrostriatal dopaminergic pathway leading to dopamine depletion is closely related to the major motor symptoms in the PD patients [2,3].

Several available PD medications to compensate dopamine levels in the brain improve symptoms at early stage of the diseases but do not stop or slow down the progression of the disease [4]. Moreover, long-term treatment of dopaminergic drugs causes undesirable side effects such as dyskinesia and wearing off [4,5]. Although many more studies are required to clear the cause of dyskinesia, therapeutic drug capable of disease modification would make possible to retard or stop severe and irreversible behavioral impairments without these adverse effects at late stage of the disease [6].

Stem cell-based therapy have been expected as a hopeful disease-

Preclinical and clinical studies for stem cells have proven to have therapeutic potential for PD. Neural precursor cells from embryonic stem cells, neural stem cells and bone marrow stem cells (BMSCs) provided therapeutic abilities when they were grafted in animal models of PD [12-14].

In recent animal studies, intravenous (IV) transplantation of human adipose-derived mesenchymal stem cell (hAdMSCs) isolated from adipose tissue showed therapeutic effects in 6-hydroxydopa-induced PD mouse by the recovery of dopaminergic neurons and the restoration of cytosolic mitochondria [15]. Both intracerebral and IV injection of hAdMSCs improved motor abilities by returning dopaminergic cell numbers to normal in 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine-induced PD mouse [16].

Stem cell therapy for the patients is limited because of concerns about safety, in particular carcinogenicity rather than efficacy of stem cells [17,18]. However, our previous retrospective research clearly demonstrated that no seriously concerned adverse effects-such as tumorigenicity were observed after multiple IV administrations of cultured hAdMSCs to normal subjects and patients for 3 years [19].

IT injection of therapeutic drugs has tried to improve therapeutic efficiency in CNS-disease-despite the inconvenience of the patient [20]. The problem remains to be solved as an administration route for stem cell therapy. Multiple IT administrations of hAdMSCs would induce unexpected side effects due to direct exposure of cultured stem cells into cerebrospinal fluid. Therefore, it is the most important to confirm safety

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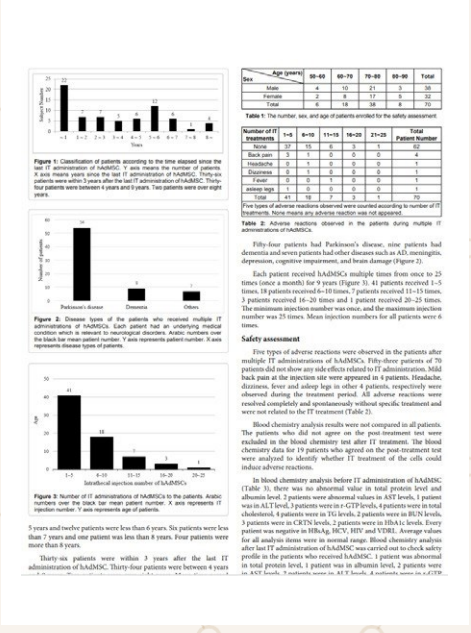


Figure 1: Classification of patients according to the time elapsed since the last IT administration of hAdMSC. Y axis means the number of patients. X axis means years since the last IT administration of hAdMSC. Thirty-six patients were within 3 years after the last IT administration of hAdMSC. Thirty-four patients were between 4 years and 9 years. Two patients were over eight years.

Figure 2: Disease types of the patients who received multiple IT administrations of hAdMSCs. Each patient had an underlying medical condition which is relevant to neurological disorders. Arabic numbers over the black bar mean patient number. Y axis represents patient number. X axis represents disease types of patients.

Figure 3: Number of IT administrations of hAdMSCs to the patients. Arabic numbers over the black bar mean patient number. X axis represents IT injection number. Y axis represents age of patients.

Sex \ Age (years)	50~59	60~79	70~89	90~99	Total
Male	4	10	21	3	38
Female	2	8	17	5	32
Total	6	18	38	8	70

Table 1: The number, sex, and age of patients enrolled for the safety assessment.

Number of IT treatments	1~5	6~10	11~15	16~20	21~25	Total Patient Number
None	37	15	6	3	1	62
Back pain	3	1	0	0	0	4
Headache	0	1	0	0	0	1
Dizziness	0	1	0	0	0	1
Fever	0	0	1	0	0	1
asleep legs	1	0	0	0	0	1
Total	41	18	7	3	1	70

Five types of adverse reactions observed were counted according to number of IT treatments. None means any adverse reaction was not appeared

Table 2: Adverse reactions observed in the patients during multiple IT administrations of hAdMSCs.

Fifty-four patients had Parkinson's disease, nine patients had dementia and seven patients had other diseases such as AD, meningitis, depression, cognitive impairment, and brain damage (Figure 2).

Each patient received hAdMSCs multiple times from once to 25 times (once a month) for 9 years (Figure 3). 41 patients received 1–5 times, 18 patients received 6–10 times, 7 patients received 11–15 times, 3 patients received 16–20 times and 1 patient received 20–25 times. The minimum injection number was once, and the maximum injection number was 25 times. Mean injection numbers for all patients were 6 times.

Safety assessment

Five types of adverse reactions were observed in the patients after multiple IT administrations of hAdMSCs. Fifty-three patients of 70 patients did not show any side effects related to IT administration. Mild back pain at the injection site were appeared in 4 patients. Headache, dizziness, fever and asleep legs in other 4 patients, respectively were observed during the treatment period. All adverse reactions were resolved completely and spontaneously without specific treatment and were not related to the IT treatment (Table 2).

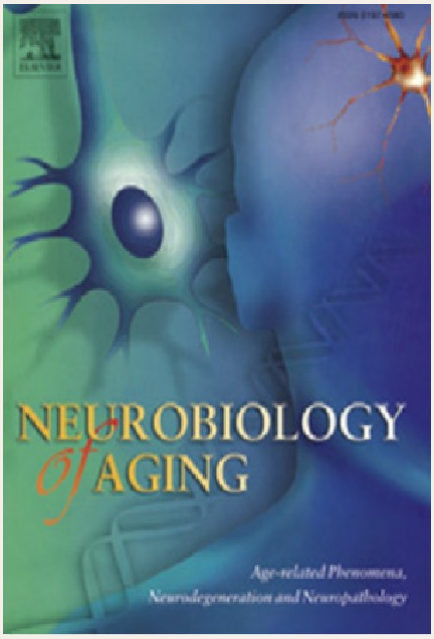
Blood chemistry analysis results were not compared in all patients. The patients who did not agree on the post-treatment test were excluded in the blood chemistry test after IT treatment. The blood chemistry data for 19 patients who agreed on the post-treatment test were analyzed to identify whether IT treatment of the cells could induce adverse reactions.

In blood chemistry analysis before IT administration of hAdMSC (Table 3), there was no abnormal value in total protein level and albumin level. 2 patients were abnormal values in AST levels, 1 patient was in ALT level, 3 patients were in γ-GTP levels, 4 patients were in total cholesterol, 4 patients were in TG levels, 2 patients were in BUN levels, 3 patients were in CRTN levels, 2 patients were in HbA1c levels. Every patient was negative in HBsAg, HCV, HIV and VDRL. Average values for all analysis items were in normal range. Blood chemistry analysis after last IT administration of hAdMSC was carried out to check safety profile in the patients who received hAdMSC. 1 patient was abnormal in total protein level, 1 patient was in albumin level, 2 patients were in AST levels, 2 patients were in ALT levels, 4 patients were in γ-GTP

Safety of Multiple Intrathecal Administrationsof Cultured Human Autologous Adipose-Derived Stem Cells in the Patients with Neuro logical Disorders Including Parkinson's Disease. (Ra, Jeon g-Chan, et al., Journalof Clinical Case Reports 8.10 118)

(Data from patients receivingstem cells manufactured by JASC and Rbio)

Biostar Stem Cell Technology Research Institute has identified to the mechanism of stem cell treatment for Parkinson's disease.



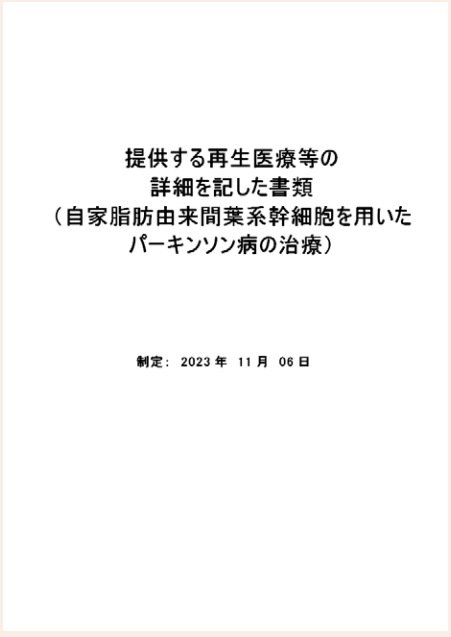

Neurobiology of Aging

Therapeutic potentials of human adipose-derived stem cells on the mouse model of Parkinson's disease

- Intravenous administration of human adipose derived stem cells was applied to the brain of an animal model of Parkinson's disease where dopamine-like neurons were restored, the number of mitochondria with altered structure was reduced, and mitochondrial complex I activity was restored. In addition, the improvement in behavioral ability was confirmed at 3 weeks of stem cell administration.
- The possibility of stem cell treatment for Parkinson's disease has been confirmed from the mitochondrial function of brain neurons being restored through the intravenous administration of human adipose- derived stem cells.

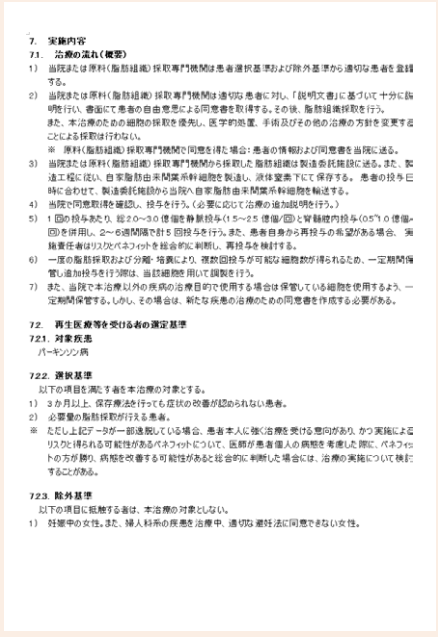
Therapeutic potentials of human adipose-derived stem cells on the mouse model of Parkinson's disease.
Neurobiol Aging. 2015 Oct;36(10):2885-92.
Choi HS, Kim HJ, Oh JH, Park HG, Ra JC, Chang KA, Suh YH.

Parkinson's Disease Regenerative Medicine Stem Cell Therapy Program Approved by Japan's Ministry of Health, Labour and Welfare



提供する再生医療等の
詳細を記した書類
（自家脂肪由来間葉系幹細胞を用いた
パーキンソン病の治療）

制定： 2023 年 11 月 06 日



7. 実施内容

7.1. 治療の流れ（概要）

1) 当院または原料（脂肪組織）採取専門機関は患者選択基準および除外基準から適切な患者を登録する。
2) 当院または原料（脂肪組織）採取専門機関は適切な患者に対し、「説明文書」に基づいて十分に説明を行い、書面にて患者の自由意思による同意書を取得する。その後、脂肪組織採取を行う。
また、本治療のための細胞の採取を優先し、医学的処置、手術及びその他の治療の方針を変更することによる採取は行わない。
※ 原料（脂肪組織）採取専門機関で同意を得た場合：患者の情報および同意書を当院に送る。
3) 当院または原料（脂肪組織）採取専門機関から採取した脂肪組織は製造委託施設に送る。また、製造工程に従い、自家脂肪由来間葉系幹細胞を製造し、液体窒素下にて保存する。患者の投与日時に合わせて、製造委託施設から当院へ自家脂肪由来間葉系幹細胞を輸送する。
4) 当院で同意取得を確認し、投与を行う。（必要に応じて治療の追加説明を行う。）
5) 1 回の投与あたり、総 2.0～3.0 億個を静脈投与（1.5～2.5 億個/回）と腎髄腔内投与（0.5～1.0 億個/回）を併用し、2～6 週間隔で計 5 回投与を行う。また、患者自身から再投与の希望がある場合、実施責任者はリスクとベネフィットを総合的に判断し、再投与を検討する。
6) 一度の脂肪採取および分離・培養により、複数回投与が可能な細胞数が得られるため、一定期間保管し追加投与を行う際は、当該細胞を用いて調製を行う。
7) また、当院で本治療以外の疾病の治療目的で使用する場合は保管している細胞を使用するよう、一定期間保管する。しかし、その場合は、新たな疾患の治療のための同意書を作成する必要がある。

7.2. 再生医療等を受ける者の選定基準

7.2.1. 対象疾患

パーキンソン病

7.2.2. 選択基準

以下の項目を満たす者を本治療の対象とする。

1) 3 か月以上、保存療法を行っても症状の改善が認められない患者。
2) 必要量の脂肪採取が行える患者。
※ ただし上記データが一部逸脱している場合、患者本人に強く治療を受ける意向があり、かつ実施によるリスクと得られる可能性があるベネフィットについて、医師が患者個人の病態を考慮した際に、ベネフィットの方が勝り、病態を改善する可能性があると総合的に判断した場合には、治療の実施について検討することがある。

7.2.3. 除外基準

以下の項目に抵触する者は、本治療の対象としない。

1) 妊娠中の女性。また、婦人科系の疾患を治療中、適切な避妊法に同意できない女性。

Parkinson's Disease Regenerative Medicine Stem Cell Therapy Program

Target Disease
Parkinson's Disease

A Single Administration of Autologous Adipose Derived Stem Cells
200 Million cells

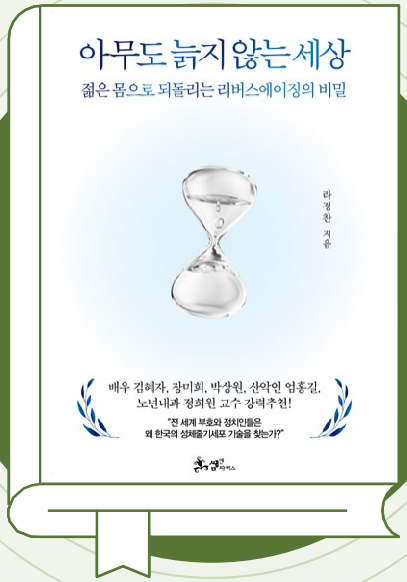
Administration Site
Intravenous, Intrathecal

Administerable cells by site
Intravenous: 150 million cells
Intrathecal: 50 million cell

Administration Interval
2 to 6 weeks apart

Number of Administration
5 sessions / 1 cycle

Based on the case of Dr. Soon Kwon Kim introduced in the book ‘A World Where No One Ages” written by Dr. Jeong Chan Ra

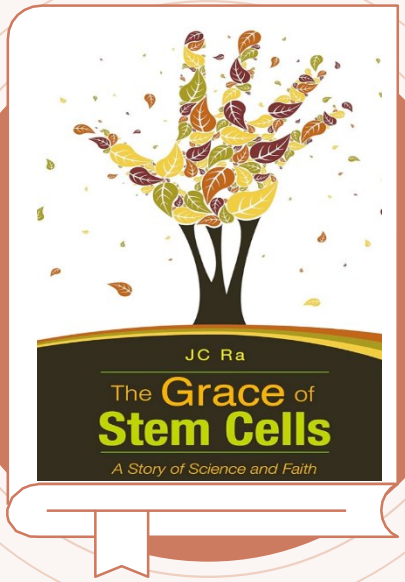


Dr. Soon Kwon Kim was diagnosed with Parkinson’s disease by a prominent neurologist in New York in 2011. The disease was progressing rapidly by the summer of 2012. He was prescribed 1,000 mg of Levodopa, the most effective medicine for Parkinson’s disease.

This is almost 2.5 times of his prescribed dose of 400 mg from just one year ago.

Once Dr. Kim began stem cell therapy, his symptoms improved, and in 2014, a year later, his prescription for Levodopa was gradually lowered from 1,000 mg to 650-700 mg.

Based on the case of Mr. Jae Sik Lee introduced in the book "The Grace of Stem Cells" written by Dr. Jeong Chan Ra



When I was diagnosed with Parkinson's disease, it reminded me of Muhammad Ali, former American professional boxer who was shaking when he appeared on TV. I was speechless and thought, "I'm going to be the same."
Regardless of my will, my right hand trembled and soon after, I even had REM sleep behavioral disorder.

Through Biostar Stem Cell Research Institute, I received intravenous administrations 4 times. There were not any differences after the first administration. However, I experie nced noticeable changes after the second administration. I experienced a decrease in t remors as well as a decrease in REM sleep disorder.
After the third and fourth administrations, I encountered remarkable changes in my body. My tremors were almost improved and REM sleep disorder was completely cured.

Reference

Treatment Strategy for Parkinsonian Diseases Through Mesenchymal Stem Cells

Hyun-Jung Park, Phil Hyu Lee Department of Neurology and Brain Research Institute, Yonsei University College of Medicine, Severance Biomedical Science Institute, Yonsei University, Seoul, Korea
Hanyang Med Rev 2012;32:145-153
http://dx.doi.org/10.7599/hmr.2012.32.3.145 pISSN 1738-429X eISSN 2234-4446

Abstract

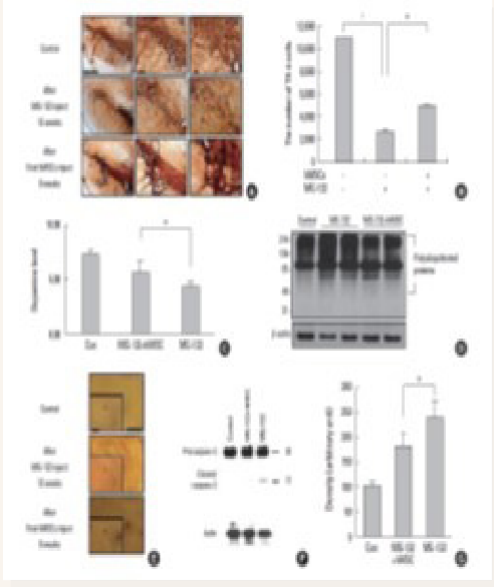
Parkinsonian diseases including Parkinson's disease (PD) and multiple system atrophy (MSA) are neurodegenerative diseases representative of α-synucleinopathies characterized pathologically by α-synuclein-abundant Lewy bodies and glial cytoplasmic inclusions, respectively. Cell therapy using mesenchymal stem cells (MSCs) is attractive clinically because these cells are free from ethical and immunological problems. MSCs are present in adult bone marrow and represent < 0.01% of all nucleated bone marrow cells. MSCs are multipotent, and differentiation under appropriate conditions into chondrocytes, skeletal myocytes, and neurons has been demonstrated thus far. According to recent studies, the neuroprotective effect of MSCs is mediated by the production of various trophic factors that contribute to functional recovery, neuronal cell survival, and endogenous regeneration of neural tissues. Additionally, MSCs appear to have immunoregulatory properties that can ameliorate the progression of disease. However, the therapeutic use of MSCs as neuroprotectives in PD and MSA has seldom been studied. Here, we comprehensively review recent advances in clinical strategies using MSCs in PD and MSA, especially focusing on their neuroprotective properties in preventing or delaying disease progression and therapeutic potential for providing functional recovery.

Reference

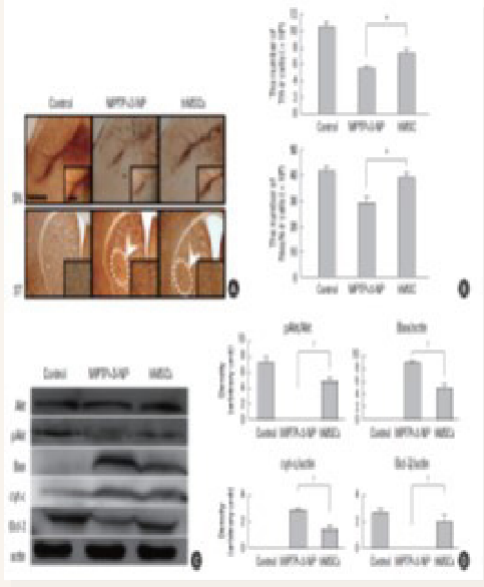
Mechanism of mesenchymal Stem Cell Treatment for Parkinson's Disease

1. Neurocellular Protection Effect of Mesenchymal Stem Cells

Effect of inhibiting the loss of dopaminergic nerve sources by secretion of neurotrophic substances (Nerve growth factor, Brain-derived neurotrophic factor, Glial cell-derived neurotrophic factor, etc.)



(Fig.1)



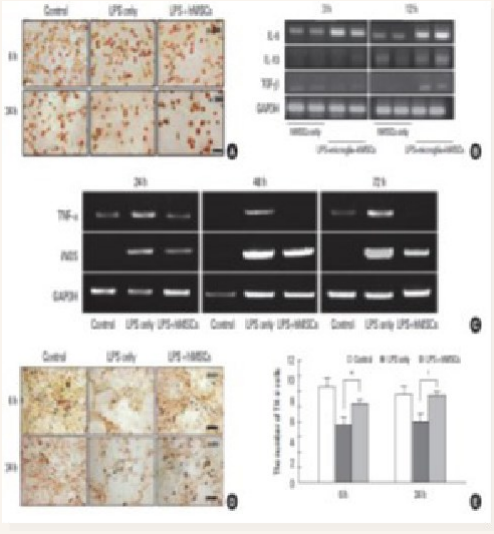
(Fig.2)

Fig.1, Fig.2 Summary

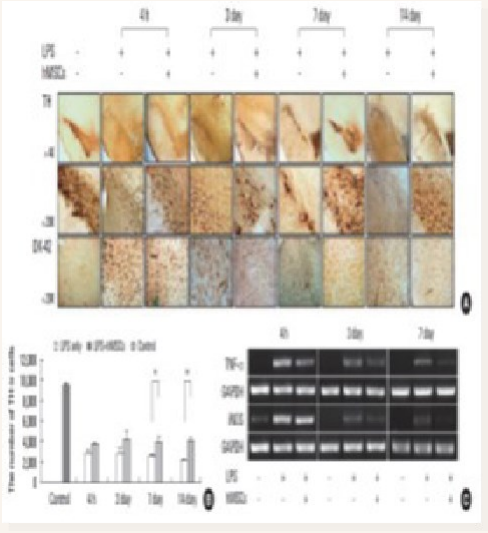
1) Reduce autologous apoptosis activation
2) Reduce the accumulation of toxic proteins
3) Reduce microglia activity

Mechanism of mesenchymal Stem Cell Treatment for Parkinson's Disease

2. Protection of dopamine-sensitive nerve sources through neuroinflammatory control effect of mesenchymal stem cells.



(Fig.3)



(Fig.4)

Fig.3, Fig.4 Summary

1) It reduces the inflammatory factors Tumor Necrosis factor (TNF)-α and induced nitric oxide synthase (iNOS).

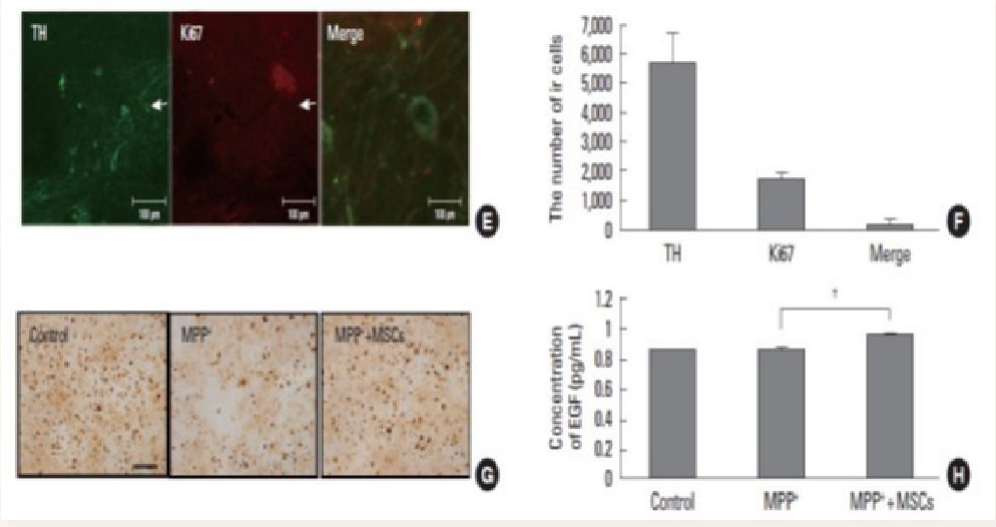
2) It increases the secretion of anti-inflammatory factors such as interleukin-6 (IL-6), IL-10, and transforming gr owth factor-β (TGF-β).

3) By inhibiting microglia activation, it reduces the death of dopaminergic neurons by more than 50%.

4) It significantly reduces the death of dopamine neurons by in vivo-activated microglia.

Mechanism of mesenchymal Stem Cell Treatment for Parkinson's Disease

3. The effect of boosting neurorenewal (Neurogenesis) of mesenchymal stem cells



(Fig.5)

Fig.5 Summary

1) It Significantly incre a sed cell regeneration in subventricular zona (SVZ) and substantia nigra (SN) in Parkinson's models.

2) Some cells that have grown in the substantia nigra differentiate into dopaminergic nerves (dopamine secretion).

3) It increases the expression of epidermal growth factor (EGF), which plays an important role in nerve regeneration.

Biostar's Motto

경천애인

敬天愛人

Love your God, Love your neighbor

Special Benefits in Celebration of the World's First Stem Cell Treatment for Parkinson's Disease Approved by MLHW of Japan

- Administration Site: Intravenous, Intrathecal
- Numeber of Administered Cells - Intravenous: 150 million cells
  - Intrathecal: 50 million cells
- Number of Administered Cells per Injection : 200 million cells
- This program consists of a total of 5 sessions held at intervals of 4 to 6 weeks, completing one cycle.

※ The cost for one cycle is USD 100,000

www.stemcellbio.com/ask@stemcellbio.com