REVIEW

Stem Cell Therapy for Neurodegenerative Diseases: Strategies for Regeneration against Degeneration

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ABSTRACT

Neurodegeneration is a general term for the progressive loss of structure and/ or function of neurons, gives rise to dysfunction or death of neurons. Neurodegenerative diseases including Alzheimer´s disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), spinal cord injury (SCI) and brain ischemia (BI) occur as a result of neurodegenerative processes leading to different degrees of paralysis and loss of sensation and cognition in the patients. Unfortunately, no successful cure for neurodegenerative disorders has been developed so far, and most of the currently available pharmacological therapies are mainly palliative. In recent years, stem cells have provided a great opportunity to develop potentially powerful innovative strategies to cure neurodegenerative diseases. Stem cells transplantation is capable of restoring injured neuronal tissue by replacement of the damaged cells via using directly differentiated cells or by protecting of existing healthy neurons and glial cells from further damage, or by repairing through providing a conductive environment in favour of regeneration. Here we have brought together some of these examples, discuss possible therapeutic means using different types of stem cells, mainly adult stem cells (ASCs), to treat neurodegenerative diseases.

Keywords: Neurological disorders, Stem cell therapy, Genetically modification, Paracrine effects, Differentiation, Combinatorial treatment, Cell cartridge

Neurodegenerative diseases are divided into acute cases, like spinal cord injury (SCI) and brain ischemia (BI), in which different types of both neurons and glial cells restricted to the stroke site are lost over a short period of time (1, 2), and chronic cases such as Alzheimer disease (AD), Parkinson

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disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), that dysfunction or death of neurons and/or glial cells happen over the years. In chronic state, degeneration process could be widespread/general (i.e. affect many types of neurons in AD) or selective involving just one specific type of cell (e.g. dopaminergic neurons in PD and motor neurons in ALS) (3-5). However, currently there are no available treatments, and drugs are entirely palliative for these diseases, finally leading to progressive loss of sensation, cognition, and motor neurons and gradual paralysis of the patient (4). Therefore, stem cells have been proposed as a promising treatment for neurodegenerative diseases (1).

Most of the studies in stem cell-based therapy for neurodegenerative diseases have been conducted preclinically in animal models which have shown stem cells could differentiation into neuronal and glial cells, promote functional recovery of nervous tissue, affect endogenous cells, decrease motor impairments by trophic support and also prevent detrimental events associated with neurodegenerative disorders (6-9). In addition, there are some evidence from clinical trials indicates the same results as preclinical studies, although they are not consistent and convincing at this time (7, 10-13). Moreover, there are many planned and ongoing clinical studies investigating different aspects of stem cell therapies for neurodegenerative disorders (please refer to https://clinicaltrials.gov), which is growing every day.

Many different sources of stem cells have been examined to determine which one is the most efficacious for stem cell therapy of neurodegenerative diseases (14-16). In addition to embryonic stem cells (ESCs), stem cells derived from adults tissues/organs are of keen interest because they are readily available sources of stem cells and easily expanded *in vitro* without ethical problems and no tumor formation report so far (17, 18). The key benefit of adult stem cells (ASCs) is that they can be harvested from various sources frequently and possibility to use in autologous therapy. This omits the risks, ethical and religious problems and immunorejection issues that allogeneic ESCs have. However, their limited differentiation potential restricts universal use of ASCs (17, 19). In recent years, extensive efforts have been carried out by investigators to successfully generate neurons and glial cells from different types of stem cells, and to exploit other beneficial aspects of stem cells to treat neurological diseases. We review here previously published experiments, animal studies and clinical trials involving stem cells based treatment for neurodegenerative diseases and discuss the potential future perspective for stem cell therapy of neurological diseases in the clinical setting.

Degenerative disorders of the central nervous system (CNS)

Central nervous system (CNS) consists of brain and spinal cord, as well as their coverings which has special features such as diverse and complex cytology and topography, axoplasmic transport, neurotransmitters, myelin, three classes of intermediate filaments (i.e. vimentin, glial fibrillary acidic protein (GFAP), and neurofilaments), separate population of interstitial cells, glia cells, cerebrospinal fluid, blood brain barrier, absent lymphatic vessels and lymph nodes, and etc. Some conditions such as programmed aging (20), disruption of extracellular matrix (ECM) (21), deterioration by oxidative stress (22), and insufficient protein degradation and subsequently accumulation of misfolded proteins (23) could give rise to synaptic loss and neural or glial cells damage in CNS. For instance, aging through loss of brain parenchyma, shrinkage of large neurons, cellular gliosis, intraneuronal (intraglial) aggregation of proteins, viruses or lysosomal substrates affects CNS to develop neurodegenerative conditions (20).

Generally, neurodegenerative diseases such as AD, PD, HD, AML and MS have unknown etiology and associated with progressive dysfunction/death of neurons or their systems due to biochemical, structural and functional changes selectively or widespread which result in dementia (memory and cognitive impairment) and/or severe motor impairment (1, 4, 20). However, understanding of disease pathology in each case would be certainly required to develop stem cell based strategic plan/s. Hence, we aimed to mention pathology of each specific disease. For instance, AD is a widespread chronic case caused by neuronal loss throughout the brain; involve the basal forebrain cholinergic system, hippocampus, amygdala and several cortical areas

(grey matter) with pathological characteristics of cortical atrophy, β-amyloid senile plaques (extraneuronal), and neurofibrillary tangles (intraneuronal) accumulation. One of possible mechanisms of synaptic and neural toxicity in Alzheimer's disease has been shown, in part, is due to β-amyloid and Tau proteins hyperphosphorylation and aggregation (4). AD is the most prevalent form of dementia. This intractable degenerative disease was first explained by German neuropathology's and psychiatrist Alois Alzheimer in 1906 and was entitled AD after him (24).

Other neurodegenerative disease, PD, is a selective chronic disease caused by the progressive death of a specific population of the cells, i.e., dopaminergic (DA) neurons in the substantia nigra and reduced DA stimulation in the striatum. PD is the second most prevalent form of dementia that like AD, researchers haven't yet found the cure of PD. People with PD use therapies that increase their dopamine levels (10). The most current effective drug for treatment of PD is levodopa (Sinemet), because it directly converted into dopamine in the brain (25).

Moreover, AML is an adult-onset neurodegenerative disorder caused by degeneration and loss of motor neurons in the cerebral cortex, brainstem and spinal cord, leading to fatal paralysis. HD is another incurable disorder which caused by expansions of polyglutamate in the huntingtin protein. HD characterized by neuronal dysfunction and degeneration contribute to the progressive physiological, cognitive, sensational and motor impairments. MS is a CNS autoimmune disease contributed to degradation of myelin that sheath affects axonal signals transport of neurons, eventually leading to progression of the disease range from fairly benign to extremely debilitating. Unlike AD, PD, HD and ALS, MS predominately affects usually young adults, and also females affected nearly twice as often as males. Again, purely symptomatic treatments are currently available for MS patients.

In addition to chronic neurodegenerative processes, acute disorders of the CNS as a result of ischemic or trauma still are a big challenge for medicine (26). Focal tissue loss caused by cerebral artery occlusion in ischemic stroke of brain leads to the death of oligodendrocytes, and astrocytes, in addition to multiple types of neurons (5). Similar situation exist in spinal cord injury (SCI) due to traumatic damage to the spinal cord which commonly caused by vehicle accidents, sports injuries, and traumatic injury in the workplace (2). Loss of oligodendrocyte and axonal demyelination are major secondary damages after injury of SCI contribute to pathological processes (27).

How regeneration works

There is homeostasis in the human body which means that the tissues/organs are able to regulate internal conditions against external changing conditions, usually by feedback controls, and stabilize whole body functioning and health (28, 29). One part of homeostasis is the periodic or constant generation of new cells to repair or replace damaged/dying cells which is called regeneration. Adult (tissue) stem cells (ASCs) normally remain quiescent unless they received activation signals to divide through a process called asymmetric cell divisions. Through this process they can maintain their populations and also differentiate into the desired cell types by creation of a progenitor (more committed cells) for tissues regeneration (29, 30).

ASCs have located in throughout the body. These stem cells reside in a particular microenvironment of tissues/organs called the "niche" which fosters the growth, proliferation and differentiation of resident stem cells. Damages to tissues, signals they receive, and changes in the stem cell niche can activate them to take part in tissue/organ regeneration (28-30).

The CNS has a limited regeneration potential which is a main challenge to develop new effective therapeutic strategies to induce its functional repair. Already, various types of stem cells have been proposed as a viable therapeutic option for degenerative diseases as they possess high proliferation capacity and able to differentiate into multiple lineages (30-32). Alternatively, through paracrine mechanisms, stem cells are also capable of influencing their microenvironment, maybe by sharing soluble secretory factors, and exosome (vesicle) containing proteins, coding RNAs and even non-coding RNAs including miRNAs and lncRNAs (29, 33, 34) (Figure 1).

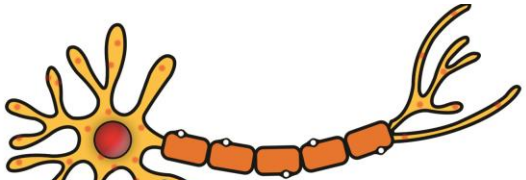

Figure 1. Mechanism of regeneration for neurodegenerative diseases by stem cells. Stem cells by asymmetric cell division proliferate, maintain cell populations, create progenitor cells, help to heal, and play a critical role in regeneration, more importantly, by secreting paracrine factors influence on neighboring cells.

There are four wide categories of stem cells considering their origin: embryonic, fetal, induced pluripotent stem (iPS) cells and ASCs (4, 30). Among ASCs, hematopoietic stem cells (HSCs) frequently found in the bone marrow, as well as in umbilical cord blood and placental tissue. They produce all the blood cell types including myeloid (e.g. macrophages, erythrocytes, monocytes, eosinophil, neutrophils, basophils, dendritic cells, and platelets) and lymphoid (i.e. B-cells, T-cells, and NK-cells) (35, 36). As it is obvious, HSCs could not be differentiated into neurons and glial cells, rather it normally used to completely replace abnormal

immune system of a patient in usually autoimmune-based disease like MS (37).

Another type of ASCs is neural stem cells (NSCs) located in (1) subventricular zone lining the lateral ventricles, and (2) subgranular zone, part of the hippocampus (38). NSCs can easily differentiate into neurons, oligodendrocytes and astrocytes (39, 40), however, they are hard to obtain, and also their *ex vivo* expansion and maintenance are hard (38, 40).

Rather than HSCs and NSCs, MSCs is considered as a more attractive type of ASCs possesses ten clinically interesting properties as shown in Figure 2. MSCs found in many adult organs but currently from bone marrow, adipose tissue, and cord blood are easiest to isolate (33). MSCs could be differentiated into cartilage cells, muscle cells, fat cells, bone cells, ligaments, tendons, and connective tissue cells. Although MSCs has mesodermal origin, interestingly they might differentiate into endodermal cell linages such as hepatocytes and ectodermal origins including neurons and glial cells (31), but with low efficacy and under special condition medium (3, 41).

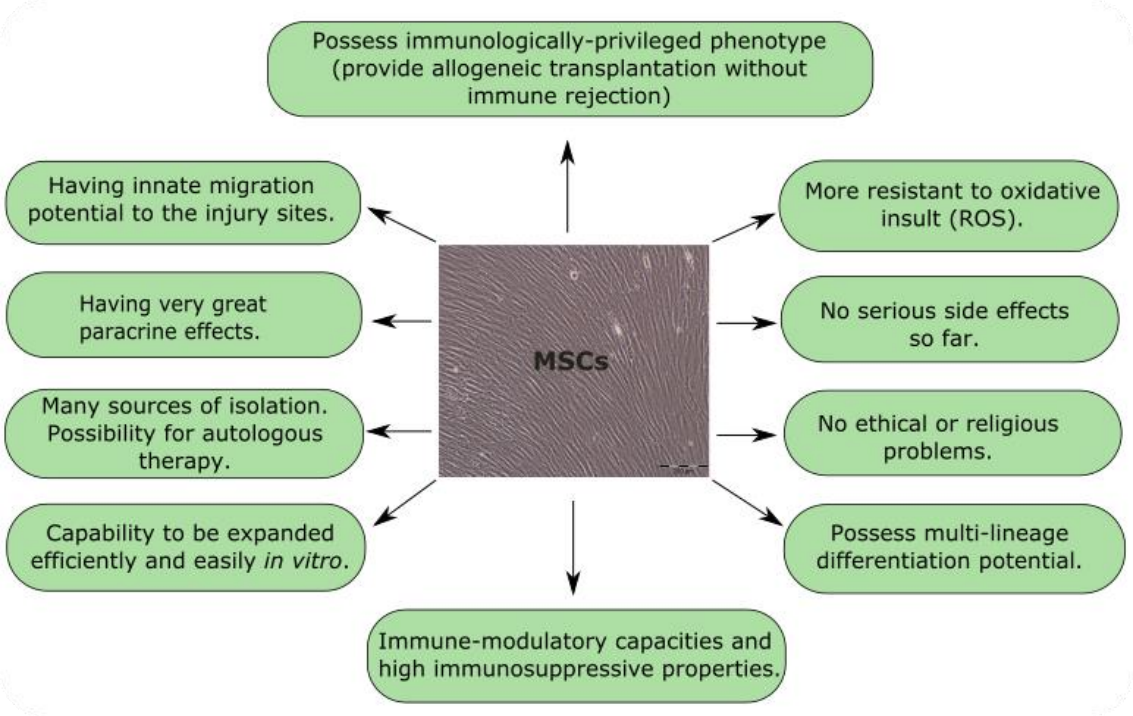

Figure 2: Ten properties of mesenchymal stem cells (MSCs) that make them more attractive for clinic. These properties represent intriguing aspect of MSCs, introducing the possibility that these cells might be used as effective therapy in neurodegenerative diseases.

Neural replacement purpose

Clinically, stem cell therapy of neurodegenerative diseases must give rise to long-lasting amendment in sensory, cognitive and motor neurons, disease symptoms, or undo disease stem cell-based therapies by replacement strategies; stem cell-based therapies by replacement strategies; generating neurons and glial cells successfully from stem cells (7, 42).

Studies have indicated that it is possible to generate all neural cell types as well as glial cells in culture from stem cells of various sources, including ESCs (43-49), iPSCs (50, 51),

NSCs (52-56), and even from the MSCs (3, 40, 57). For example, for stem cell therapy of PD, dopaminergic (DA) neurons with the properties of substantia nigra neurons have been generated from human ESCs by several studies (58-60). More recently, Hwang et al. have shown that ESC-derived neural progenitor cells (NPCs) cultured in media

supplemented with sonic hedgehog (SHH) and retinoic acid (RA) could be efficiently differentiated into DA neurons and following transplantation in SCI rat model, dramatically attenuate the chronic neuropathic pain (61). Additionally, there are several great review article about clinical trials have examined transplantation of human fetal DA neurons or NSCs; suggesting that cell replacement strategy can produce long-lasting improvement in PD patients (62, 63).

In another study, ESC-derived NPCs genetically modified by brain-derived neurotrophic factor (BDNF) to promote differentiation into the GABAergic neurons which are suitable to treatment of PD and SCI (64). Recently, allograft of ESC-derived NSCs/NPCs into the cerebrospinal fluid of nonhuman primate model of SCI led to improved motor function, but whether these neurons could integrate into existing circuitries has not been yet determined (65). Importantly, Pan et al. by studying axonogenesis of ES-derived motor neurons have shown that aberrant axon morphology was still present after engraftment of GFP- positive neurons into the SCI, suggesting that even a mature neural environment may fail to provide a proper niche to guide normal axon formation. These findings emphasis necessity for exanimating the functionality and morphogenesis of neurons before the clinical trials using ESCs or ASCs (66). First-in-human (FIH) trials have received approval in the United States in January 2009 to initiate a clinical trial assessing a human ESCs-derived oligodendrocyte, named GRNOPC1, by the Geron Corporation, for treatment of severe SCI (67). Chapman et al. have evaluated the ethical issues raised by the Geron FIH trial and then recommended ways to improve future proposed trials with novel stem cell therapies (67).

As mentioned above some examples, for replacement therapy, most of studies have used ESCs, or NSCs; however, several attempts have been done to induce MSCs towards neural and glial cells aim to use them as a neural replacement strategy (57, 68-71). For instance, to solve the problems of low differentiation rate of MSCs, Dezawa et al. efficiently induce differentiation of both rat and human BM-MSCs into neuronal cells using gene transfection with Notch intracellular domain (NICD) and subsequent treatment with trophic factor such as bFGF, forskolin, and ciliary neurotrophic factor (CNTF). Interestingly, further pretreatment of the induced neuronal cells with GDNF generated more specialized population, i.e. tyrosinehydroxylase $(TH)^+$ cells and DA neurons. Following intrastriatal transplantation of these GDNF-treated cells, behavioural improvements appeared in animal model of PD (57).

In other study, it has been revealed that rat BM-MSCs induced by treatment of bFGF and neurotrophin 3 (NT-3) can transdifferentiate into neural-like cells in culture (68). Additionally, it has been further demonstrated human BM-MSCs under conditions of cocultured with olfactory ensheathing cells (OECs) and daily supplement of bFGF could be differentiation into neural-like cells (71).

Paracrine effects and trophic supports

Whereas neuronal and glial cells replacement in neurodegenerative disease seems to be a long-way goal, using stem cells to prevent CNS cells from dying is a more realistic and short-term approach to reach clinic. This perspective is supported by the fact that most of clinical trials (107 out of 190) focused on using MSCs injection into the CNS to treat neurodegenerative diseases, traumatic spinal cord injury and brain ischemia, mainly by beneficial paracrine effects of these cells (Table 1).

Unlike studies using other stem cells, MSCs have been transplanted without prior *in vitro* differentiation in most studies aimed to use its beneficial paracrine effects. As a proof of the concept, Vercelli et al. demonstrated that human MSCs are a good candidate for ALS cell therapy because they can migrate and survive after transplantation in the lumbar spinal cord; prevent microglial activation and astrogliosis, decrease motor neuron cell death through paracrine actions, thus ameliorate the motor performance in an experimental ALS model (72).

Table 1. Clinical trials that have been conducted using stem cells to treat various neurodegenerative diseases. The number clinical trials targeting treatment of these diseases by stem cells have been presented in this table. Up to now, more than 190 clinical trials worldwide (completed, planned, and ongoing) have applied different types of stem cells, mainly MSCs, as treatment for a neurodegenerative disease including Alzheimer´s disease (AD), Huntington's disease (HD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), spinal cord injury (SCI) and brain ischemia (BI). The data collected from https://clinicaltrials.gov on 1th, January, 2016.

However, more recently, Mazzini et al. presented the results of a long-term follow-up of 19 ALS patients using autologous MSCs transplanted into the dorsal spinal cord which showed no obvious clinical benefits (73). Recently, Salem et al. have explored the possible therapeutic potential of single intravenous (IV) injection of BM-MSCs in treatment of AD experimental model compared with 2 conventional therapies of AD; cerebrolysin and rivastigmine administered daily. They observed significant improvement BM-MSCs after 4 months against AD rather than the reference drugs, suggesting that paracrine properties have important therapeutic roles. In addition, histopathological examination showed that BM-MSCs could remove beta-amyloid plaques from hippocampus (74). Moreover, it has been revealed that BM-MSCs were able to migrate on the brain and remove β-amyloid senile plaques from the hippocampus and reduce β-amyloid depositions by the activation of endogenous microglia in an AD mouse model (74, 75). Similarly, in additional studies, it has been shown that hMSCs reduce deposition of β-amyloid, improve synaptic transmission and memory deficits (76, 77).

Recently, the potential efficacy of adipose tissue-derived hMSCs in treatment of HD has been also confirmed. They observed that even xenotransplantation of human AT-MSCs could be counteracted neurodegeneration caused by HD and ameliorate some behavioral impairments (78). In a clinical study, followed-up to 5 years, intravenous autologous MSCs transplantation showed safe for ischemic stroke patients. Interestingly, clinical improvements had been associated with serum levels of stromal cell-derived factor-1(SDF-1) and the degree of involvement of the subventricular region of the lateral ventricle, showing that recovery after stroke is depend on the specific characteristics of the patients (79).

Many other studies have shown that MSCs primarily through paracrine actions can promote endogenous neurogenesis (80-82), decrease apoptosis of bystander cells (81, 83), reduce levels of free radicals especially in ischemic condition (84), encourage neurorestoration (85, 86), modulate inflammation (87-89) and etc.

Also, NSCs has been demonstrated that act through neurotrophic factors and promote axonal growth in spinal cord injury (90-92). For instance, a study has been shown that hESC-derived NPCs transplanted into the cerebral ventricles of an MS mouse model exert therapeutic benefits by immunosuppressive neuroprotective mechanism. This animal experiment may serve as a first step forward to further developments of hESC for stem cell therapy in MS (93).

Additionally, many experimental studies have shown the beneficial neuroprotective effect of HSCs-releasing factors such as erythropoietin (EPO),

granulocyte colony-stimulating factor (G-CSF), stem cell factor (SCF), VEGF, and SDF-1-alpha (94, 95). Interestingly, HSCs have innate tropism towards the site of inury (96), could be exploited this features for delivering neurothrophic and protective factors.

Genetically modification of stem cells to get better outcomes

The efficacy of both differentiation and paracrine approach could be improved by genetically modifying the stem cells for carrying new genes to better differentiate towards neuronal lineages or to secrete a specific therapeutic molecules in addition to their innate trophic support (97, 98). Stem cells naturally produce various neurotrophic factors, such as BDNF, nerve growth factor (NGF), cerebral dopamine neurotrophic factor (CDNF) or GDNF, and facilitate neuronal differentiation and maintenance of endogenous stem cells of CNS (83, 85, 99-101). For instance, transplantation of genetically engineered MSCs overexpressing BDNF showed stronger therapeutic benefits following transplantation in cerebral ischemia animal models rather than MSCs alone (102-104). The strategies to exploit therapeutic effects of stem cells have been shown in Figure 3.

Alternatively, stem cells could be genetically engineered to have high migratory ability following transplantation to delivery of factors that can modify the course of the disease by their innate trophic support (105, 106).

Furthermore, as understanding of the pathology of the specific disease is key factor to develop stem cell based treatments for neurodegenerative diseases, many studies directed to genetically modified stem cells to express disease-relevant genes (107, 108). Therefore, creating model system have advantages of investigating basic issues of neural development and cell replacement, gene therapy, disease-specific cellular pathways and testing new therapeutic approaches; would accelerate way to reach clinical (107, 109-111).

Stem cells in combination with other drug or treatment

There is still no cure for neurodegenerative diseases since the precise mechanisms of these diseases are largely unknown. However, advantages of stem cells due to the restorative and trophic abilities are far beyond drugs (108, 112).

To develop successful and more effective stem cell-based therapy for neurodegenerative diseases, several studies have suggested that it would likely require that the stem cells based therapy complement with other drugs or treatments, such as antioxidants and/or therapeutic molecules (108, 113, 114). For instance, it has been demonstrated that antioxidants such as vitamin E thorough reducing ROS levels, and protecting against peroxidation of lipids in the brain could reduce the risk of AD (113).

Many of neurodegenerative diseases are characterized by the accumulation of disease-specific misfolded proteins in the CNS (23, 115, 116). Therefore, for instance, limited proteolysis and clearance of β-amyloid plaques by activation of Cathepsin B could be offered a complement therapeutic strategy with stem cells to get better results for AD (117).

Stem cells as a cartridge

It has been suggested that the prolonged and controlled delivery of GDNF, one of the neurotrophic factors for dopamine and motor neurons recovery, into the brain could be used to long-term and more effective therapy of neurodegenerative disorders like PD (118). However, as GDNF is a large peptide, it cannot efficiently enter the brain from blood and cerebrospinal fluid (CSF) (119, 120). Therefore, it needs to be directly delivered to tissue. Possible solutions might be direct infusion into brain tissue with pumps (118, 121), delivery by injection of virus producing GDNF (122), delivery by using encapsulated cells secreting GDNF (123, 124) and delivery using stem cells secreting GDNF (125-128).

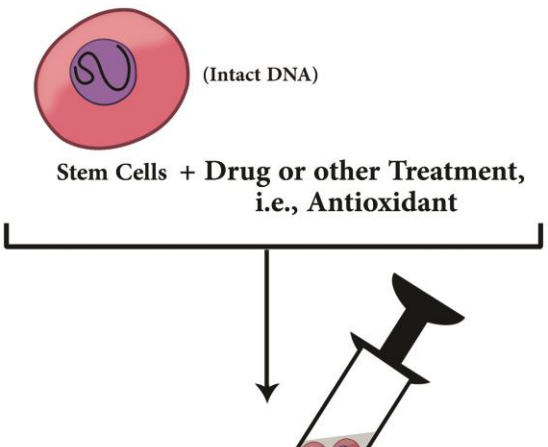

Figure 3: Strategies and innovations to get better outcomes in treatment of neurodegenerative disease by stem cell therapy. In addition to other drug or treatment, approaches could be used innate trophic actions of stem cells. Furthermore, stem cells could be genetically engineered to secret a specific therapeutic factor into site of neural damage by a novel carrier system like a cartridge. The engineered cells could be deliver new therapeutic genes, differentiation induction genes or migration-induced gene or a missing/disease-relevant gene product.

Alternatively, the novel cartridge based bioreactors have been developed in supporting liver cells with good viability and functional performance which can be an effective design for delivering trophic factors. Recently, Niu et al. have developed a machine that controls the flow of blood through the cartridge which contains billions of liver cells used as a bioartificial liver (129). The significance of these devices is that they supply an environment to maintain cells in a way that allows performing key cellular and tissue functions. In a study, expanded human BM-MSCs have been used as a cartridge system to work like a bioartificial liver (130). Therefore, this innovative approach could be exploited for neurodegenerative diseases either. However, the main drawback of this technique is impossibility to maintain cell viability effectively for the long period of time.

Conclusion

The use of stem cells, although in its early stages, appears likely to contribute to future clinical treatments of neurodegenerative disease through replacement of dysfunctional or dying neurons as well as neuroprotective and neurorestorative approaches.

Stem cells from a variety of sources have shown effective in improving motor function after

neurodegenerative diseases in animal experiments, but still need further investigation in clinical trials. Regardless of differentiation potential among different stem cells, MSCs due to having great paracrine properties are of keen interest to use in clinical settings. Furthermore, combinatorial administration of other drugs/therapeutic molecules with stem cells is proposed as a desirable approach especially to complement the gaps yet existing by the single therapeutic application of stem cells neurodegenerative disorders.

Transplantation of stem cells or stem cell-derived motor neurons or glial cells in neurodegenerative diseases in a clinical setting to replaces lost neurons, and integrates into existing neural circuitry neuronal by replacement strategy seems to be currently unrealistic and long-distant goal. Rather, using stem cells for the delivery of trophic factors to prevent disease progression seems to be a more realistic and short-term achievable goal for clinic. However, factors that control the differentiation, survival, and maturation of stem cells in the context of degenerative diseases must be more thoroughly understood before stem cell therapy that could be transferred to clinic.

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References

1. Wu Y-P, Chen W-S, Teng C, Zhang N. Stem cells for the treatment of neurodegenerative diseases. Molecules. 2010;15(10):6743-58.
2. Schroeder J, Kueper J, Leon K, Liebergall M. Stem cells for spine surgery. World journal of stem cells. 2015 Jan 26;7(1):186-94. PMID: 25621119. DOI: 10.4252/wjsc.v7.i1.186.
3. Tanna T, Sachan V. Mesenchymal stem cells: potential in treatment of neurodegenerative diseases. Current stem cell research & therapy. 2014;9(6):513-21. PMID: 25248677.
4. Dantuma E, Merchant S, Sugaya K. Stem cells for the treatment of neurodegenerative diseases. Stem Cell Res Ther. 2010;1(5):37.
5. Lindvall O, Kokaia Z. Stem cells in human neurodegenerative disorders--time for clinical translation? The Journal of clinical investigation. 2010 Jan;120(1):29-40. PMID: 20051634. DOI: 10.1172/jci40543.
6. Bjorklund A, Lindvall O. Cell replacement therapies for central nervous system disorders. Nature neuroscience. 2000;3:537-44.
7. Nicaise C, Mitrecic D, Falnikar A, Lepore AC. Transplantation of stem cell-derived astrocytes for the treatment of amyotrophic lateral sclerosis and spinal cord injury. World journal of stem cells. 2015 Mar 26;7(2):380-98. PMID: 25815122. DOI: 10.4252/wjsc.v7.i2.380.
8. Chen BK, Staff NP, Knight AM, Nesbitt JJ, Butler GW, Padley DJ, Parisi JE, Dietz AB, Windebank AJ. A safety study on intrathecal delivery of autologous mesenchymal stromal cells in rabbits directly supporting Phase I human trials. Transfusion. 2015 May;55(5):1013-20. PMID: 25413276. DOI: 10.1111/trf.12938.
9. Lee HJ, Kim KS, Ahn J, Bae HM, Lim I, Kim SU. Human motor neurons generated from neural stem cells delay clinical onset and prolong life in ALS mouse model. PloS one. 2014;9(5):e97518. PMID: 24844281. DOI: 10.1371/journal.pone.0097518.
10. Fu MH, Li CL, Lin HL, Chen PC, Calkins MJ, Chang YF, Cheng PH, Yang SH. Stem cell transplantation therapy in Parkinson's disease. SpringerPlus. 2015;4:597. PMID: 26543732. DOI: 10.1186/s40064-015-1400-1.
11. Barker RA. Developing stem cell therapies for Parkinson's disease: waiting until the time is right. Cell Stem Cell. 2014 Nov 6;15(5):539-42. PMID: 25517462. DOI: 10.1016/j.stem.2014.09.016.
12. Oh KW, Moon C, Kim HY, Oh SI, Park J, Lee JH, Chang IY, Kim KS, Kim SH. Phase I trial of repeated intrathecal autologous bone marrow-derived mesenchymal stromal cells in amyotrophic lateral sclerosis. Stem cells translational medicine. 2015 Jun;4(6):590-7. PMID: 25934946. DOI: 10.5966/sctm.2014-0212.
13. Fornai F, Meininger V, Silani V. Future therapeutical strategies dictated by pre-clinical evidence in ALS. Archives italiennes de biologie. 2011 Mar;149(1):169-74. PMID: 21412723. DOI: 10.4449/aib.v149i1.1269.
14. Yoo J, Kim HS, Hwang DY. Stem cells as promising therapeutic options for neurological disorders. Journal of cellular biochemistry. 2013 Apr;114(4):743-53. PMID: 23097262. DOI: 10.1002/jcb.24427.
15. De Feo D, Merlini A, Laterza C, Martino G. Neural stem cell transplantation in central nervous system disorders: from cell replacement to neuroprotection. Current opinion in neurology. 2012 Jun;25(3):322-33. PMID: 22547103. DOI: 10.1097/WCO.0b013e328352ec45.
16. Lescaudron L, Boyer C, Bonnamain V, Fink KD, Leveque X, Rossignol J, Nerriere-Daguin V, Malouet AC, Lelan F, Dey ND, Michel-Monigadon D, Lu M, Neveu I, von Horsten S, Naveilhan P, Dunbar GL. Assessing the potential clinical utility of transplantations of neural and

mesenchymal stem cells for treating neurodegenerative diseases. Methods in molecular biology (Clifton, NJ). 2012;879:147-64. PMID: 22610559. DOI: 10.1007/978-1-61779-815-3_10.
17. Sousa BR, Parreira RC, Fonseca EA, Amaya MJ, Tonelli FM, Lacerda SM, Lalwani P, Santos AK, Gomes KN, Ulrich H, Kihara AH, Resende RR. Human adult stem cells from diverse origins: an overview from multiparametric immunophenotyping to clinical applications. Cytometry Part A : the journal of the International Society for Analytical Cytology. 2014 Jan;85(1):43-77. PMID: 24700575. DOI: 10.1002/cyto.a.22402.
18. Stoll EA. Advances toward regenerative medicine in the central nervous system: challenges in making stem cell therapy a viable clinical strategy. Molecular and cellular therapies. 2014;2:12. PMID: 26056581. DOI: 10.1186/2052-8426-2-12.
19. Rice CM, Scolding NJ. Autologous bone marrow stem cells--properties and advantages. Journal of the neurological sciences. 2008 Feb 15;265(1-2):59-62. PMID: 17669432. DOI: 10.1016/j.jns.2007.06.011.
20. Castorina A, Szychlinska MA, Marzagalli R, Musumeci G. Mesenchymal stem cells-based therapy as a potential treatment in neurodegenerative disorders: is the escape from senescence an answer? Neural regeneration research. 2015 Jun;10(6):850-8. PMID: 26199588. DOI: 10.4103/1673-5374.158352.
21. Bonneh-Barkay D, Wiley CA. Brain extracellular matrix in neurodegeneration. Brain pathology (Zurich, Switzerland). 2009 Oct;19(4):573-85. PMID: 18662234. DOI: 10.1111/j.1750-3639.2008.00195.x.
22. Kim GH, Kim JE, Rhie SJ, Yoon S. The Role of Oxidative Stress in Neurodegenerative Diseases. Experimental neurobiology. 2015 Dec;24(4):325-40. PMID: 26713080. DOI: 10.5607/en.2015.24.4.325.
23. van Ham TJ, Breitling R, Swertz MA, Nollen EA. Neurodegenerative diseases: Lessons from genome-wide screens in small model organisms. EMBO molecular medicine. 2009 Nov;1(8-9):360-70. PMID: 20049741. DOI: 10.1002/emmm.200900051.
24. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. Neurobiology of aging. 1998 May-Jun;19(3):173-89. PMID: 9661992.
25. Rezak M. Current pharmacotherapeutic treatment options in Parkinson's disease. Disease-a-month : DM. 2007 Apr;53(4):214-22. PMID: 17586328. DOI: 10.1016/j.disamonth.2007.05.002.
26. Mejia-Toiber J, Castillo CG, Giordano M. Strategies for the development of cell lines for ex vivo gene therapy in the central nervous system. Cell transplantation. 2011;20(7):983-1001. PMID: 21176399. DOI: 10.3727/096368910x546599.
27. Li N, Leung GK. Oligodendrocyte Precursor Cells in Spinal Cord Injury: A Review and Update. BioMed research international. 2015;2015:235195. PMID: 26491661. DOI: 10.1155/2015/235195.
28. Wilson A, Trumpp A. Bone-marrow haematopoietic-stem-cell niches. Nature reviews Immunology. 2006 Feb;6(2):93-106. PMID: 16491134. DOI: 10.1038/nri1779.
29. Ghorbani A, Naderi-Meshkin H. The endocrine regulation of stem cells: physiological importance and pharmacological potentials for cell-based therapy. Current stem cell research & therapy. 2015 Sep 4. PMID: 26337380.
30. Girlovanu M, Susman S, Soritau O, Rus-Ciuca D, Melincovici C, Constantin AM, Mihu CM. Stem cells - biological update and cell therapy progress. Clujul medical (1957). 2015;88(3):265-71. PMID: 26609255. DOI: 10.15386/cjmed-483.
31. Lavoie JR, Rosu-Myles M. Uncovering the secretes of mesenchymal stem cells. Biochimie. 2013 Dec;95(12):2212-21. PMID: 23810910. DOI: 10.1016/j.biochi.2013.06.017.
32. Mattson MP. Stem cells as therapeutics for neurodegenerative disorders? Expert review of neurotherapeutics. 2001 Nov;1(2):267-73. PMID: 19811037. DOI: 10.1586/14737175.1.2.267.
33. Maumus M, Jorgensen C, Noel D. Mesenchymal stem cells in regenerative medicine applied to rheumatic diseases: role of secretome and exosomes. Biochimie. 2013 Dec;95(12):2229-34. PMID: 23685070. DOI: 10.1016/j.biochi.2013.04.017.
34. Teixeira FG, Carvalho MM, Sousa N, Salgado AJ. Mesenchymal stem cells secretome: a new paradigm for central nervous system regeneration? Cellular and molecular life sciences : CMLS. 2013 Oct;70(20):3871-82. PMID: 23456256. DOI: 10.1007/s00018-013-1290-8.
35. Fassas A, Kazis A. High-dose immunosuppression and autologous hematopoietic stem cell rescue for severe multiple sclerosis. Journal of hematotherapy & stem cell research. 2003 Dec;12(6):701-11. PMID: 14977479. DOI: 10.1089/15258160360732722.
36. Barzilay R, Levy YS, Melamed E, Offen D. Adult stem cells for neuronal repair. The Israel Medical Association journal : IMAJ. 2006 Jan;8(1):61-6. PMID: 16450758.
37. Harrison DM, Calabresi PA. Promising treatments of tomorrow for multiple sclerosis. Annals of Indian Academy of Neurology. 2009 Oct;12(4):283-90. PMID: 20182576. DOI: 10.4103/0972-2327.58279.
38. Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron. 2011 May 26;70(4):687-702. PMID: 21609825. DOI: 10.1016/j.neuron.2011.05.001.
39. Cao QL, Zhang YP, Howard RM, Walters WM, Tsoulfas P, Whittemore SR. Pluripotent stem cells engrafted into the normal or lesioned adult rat spinal cord

are restricted to a glial lineage. Experimental neurology. 2001 Jan;167(1):48-58. PMID: 11161592. DOI: 10.1006/exnr.2000.7536.

40. Jiang Y, Zhang MJ, Hu BY. Specification of functional neurons and glia from human pluripotent stem cells. Protein & cell. 2012 Nov;3(11):818-25. PMID: 23143871. DOI: 10.1007/s13238-012-2086-6.

41. Zhao Y, Jiang H, Liu XW, Xiang LB, Zhou DP, Chen JT. MiR-124 promotes bone marrow mesenchymal stem cells differentiation into neurogenic cells for accelerating recovery in the spinal cord injury. Tissue & cell. 2015 Apr;47(2):140-6. PMID: 25697062. DOI: 10.1016/j.tice.2015.01.007.

42. Hovakimyan M, Haas SJ, Schmitt O, Gerber B, Wree A, Andressen C. Mesencephalic human neural progenitor cells transplanted into the neonatal hemiparkinsonian rat striatum differentiate into neurons and improve motor behaviour. Journal of anatomy. 2006 Dec;209(6):721-32. PMID: 17118060. DOI: 10.1111/j.1469-7580.2006.00654.x.

43. Bjorklund LM, Sanchez-Pernaute R, Chung S, Andersson T, Chen IY, McNaught KS, Brownell AL, Jenkins BG, Wahlestedt C, Kim KS, Isacson O. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proceedings of the National Academy of Sciences of the United States of America. 2002 Feb 19;99(4):2344-9. PMID: 11782534. DOI: 10.1073/pnas.022438099.

44. Cho MS, Hwang DY, Kim DW. Efficient derivation of functional dopaminergic neurons from human embryonic stem cells on a large scale. Nature protocols. 2008;3(12):1888-94. PMID: 19008875. DOI: 10.1038/nprot.2008.188.

45. Cho MS, Lee YE, Kim JY, Chung S, Cho YH, Kim DS, Kang SM, Lee H, Kim MH, Kim JH, Leem JW, Oh SK, Choi YM, Hwang DY, Chang JW, Kim DW. Highly efficient and large-scale generation of functional dopamine neurons from human embryonic stem cells. Proceedings of the National Academy of Sciences of the United States of America. 2008 Mar 4;105(9):3392-7. PMID: 18305158. DOI: 10.1073/pnas.0712359105.

46. Singh Roy N, Nakano T, Xuing L, Kang J, Nedergaard M, Goldman SA. Enhancer-specified GFP-based FACS purification of human spinal motor neurons from embryonic stem cells. Experimental neurology. 2005 Dec;196(2):224-34. PMID: 16198339. DOI: 10.1016/j.expneurol.2005.06.021.

47. Soundararajan P, Lindsey BW, Leopold C, Rafuse VF. Easy and rapid differentiation of embryonic stem cells into functional motoneurons using sonic hedgehog-producing cells. Stem cells (Dayton, Ohio). 2007 Jul;25(7):1697-706. PMID: 17395777. DOI: 10.1634/stemcells.2006-0654.

48. Lee H, Shamy GA, Elkabetz Y, Schofield CM, Harrsion NL, Panagiotakos G, Socci ND, Tabar V, Studer L. Directed differentiation and transplantation of human embryonic stem cell-derived motoneurons. Stem cells (Dayton, Ohio). 2007 Aug;25(8):1931-9. PMID: 17478583. DOI: 10.1634/stemcells.2007-0097.

49. Li XJ, Du ZW, Zarnowska ED, Pankratz M, Hansen LO, Pearce RA, Zhang SC. Specification of motoneurons from human embryonic stem cells. Nature biotechnology. 2005 Feb;23(2):215-21. PMID: 15685164. DOI: 10.1038/nbt1063.

50. Wernig M, Zhao JP, Pruszak J, Hedlund E, Fu D, Soldner F, Broccoli V, Constantine-Paton M, Isacson O, Jaenisch R. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. Proceedings of the National Academy of Sciences of the United States of America. 2008 Apr 15;105(15):5856-61. PMID: 18391196. DOI: 10.1073/pnas.0801677105.

51. Dimos JT, Rodolfa KT, Niakan KK, Weisenthal LM, Mitsumoto H, Chung W, Croft GF, Saphier G, Leibel R, Goland R, Wichterle H, Henderson CE, Eggan K. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. Science (New York, NY). 2008 Aug 29;321(5893):1218-21. PMID: 18669821. DOI: 10.1126/science.1158799.

52. Sanchez-Pernaute R, Studer L, Bankiewicz KS, Major EO, McKay RD. In vitro generation and transplantation of precursor-derived human dopamine neurons. Journal of neuroscience research. 2001 Aug 15;65(4):284-8. PMID: 11494363.

53. Studer L, Tabar V, McKay RD. Transplantation of expanded mesencephalic precursors leads to recovery in parkinsonian rats. Nat Neurosci. 1998 Aug;1(4):290-5. PMID: 10195162. DOI: 10.1038/1105.

54. Parish CL, Castelo-Branco G, Rawal N, Tonnesen J, Sorensen AT, Salto C, Kokaia M, Lindvall O, Arenas E. Wnt5a-treated midbrain neural stem cells improve dopamine cell replacement therapy in parkinsonian mice. The Journal of clinical investigation. 2008 Jan;118(1):149-60. PMID: 18060047. DOI: 10.1172/jci32273.

55. Bohl D, Liu S, Blanchard S, Hocquemiller M, Haase G, Heard JM. Directed evolution of motor neurons from genetically engineered neural precursors. Stem cells (Dayton, Ohio). 2008 Oct;26(10):2564-75. PMID: 18635866. DOI: 10.1634/stemcells.2008-0371.

56. Jordan PM, Ojeda LD, Thonhoff JR, Gao J, Boehning D, Yu Y, Wu P. Generation of spinal motor neurons from human fetal brain-derived neural stem cells: role of basic fibroblast growth factor. Journal of neuroscience research. 2009 Feb;87(2):318-32. PMID: 18803285. DOI: 10.1002/jnr.21856.

57. Dezawa M, Kanno H, Hoshino M, Cho H, Matsumoto N, Itokazu Y, Tajima N, Yamada H, Sawada H, Ishikawa H, Mimura T, Kitada M, Suzuki Y, Ide C. Specific induction of neuronal cells from bone marrow

stromal cells and application for autologous transplantation. The Journal of clinical investigation. 2004 Jun;113(12):1701-10. PMID: 15199405. DOI: 10.1172/jci20935.
58. Fricker-Gates RA, Gates MA. Stem cell-derived dopamine neurons for brain repair in Parkinson's disease. Regen Med. 2010 Mar;5(2):267-78. PMID: 20210586. DOI: 10.2217/rme.10.3.
59. Roy NS, Cleren C, Singh SK, Yang L, Beal MF, Goldman SA. Functional engraftment of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes. Nature medicine. 2006 Nov;12(11):1259-68. PMID: 17057709. DOI: 10.1038/nm1495.
60. Yang D, Zhang ZJ, Oldenburg M, Ayala M, Zhang SC. Human embryonic stem cell-derived dopaminergic neurons reverse functional deficit in parkinsonian rats. Stem cells (Dayton, Ohio). 2008 Jan;26(1):55-63. PMID: 17951220. DOI: 10.1634/stemcells.2007-0494.
61. Hwang I, Hahm SC, Choi KA, Park SH, Jeong H, Yea JH, Kim J, Hong S. Intrathecal Transplantation of Embryonic Stem Cell-Derived Spinal GABAergic Neural Precursor Cells Attenuates Neuropathic Pain in a Spinal Cord Injury Rat Model. Cell transplantation. 2015 Sep 16. PMID: 26407027. DOI: 10.3727/096368915x689460.
62. Wijeyekoon R, Barker RA. Cell replacement therapy for Parkinson's disease. Biochimica et biophysica acta. 2009 Jul;1792(7):688-702. PMID: 19007882. DOI: 10.1016/j.bbadis.2008.10.007.
63. Lindvall O. Treatment of Parkinson's disease using cell transplantation. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 2015 Oct 19;370(1680):20140370. PMID: 26416681. DOI: 10.1098/rstb.2014.0370.
64. Nefzger CM, Su CT, Fabb SA, Hartley BJ, Beh SJ, Zeng WR, Haynes JM, Pouton CW. Lmx1a allows context-specific isolation of progenitors of GABAergic or dopaminergic neurons during neural differentiation of embryonic stem cells. Stem cells (Dayton, Ohio). 2012 Jul;30(7):1349-61. PMID: 22495882. DOI: 10.1002/stem.1105.
65. Iwai H, Shimada H, Nishimura S, Kobayashi Y, Itakura G, Hori K, Hikishima K, Ebise H, Negishi N, Shibata S, Habu S, Toyama Y, Nakamura M, Okano H. Allogeneic Neural Stem/Progenitor Cells Derived From Embryonic Stem Cells Promote Functional Recovery After Transplantation Into Injured Spinal Cord of Nonhuman Primates. Stem cells translational medicine. 2015 Jul;4(7):708-19. PMID: 26019226. DOI: 10.5966/sctm.2014-0215.
66. Pan HC, Wu YT, Shen SC, Wang CC, Tsai MS, Cheng FC, Lin SZ, Chen CW, Liu CS, Su HL. Characterization of axon formation in the embryonic stem cell-derived motoneuron. Cell transplantation. 2011;20(4):493-502. PMID: 21054941. DOI: 10.3727/096368910x536464.
67. Chapman AR, Scala CC. Evaluating the first-in-human clinical trial of a human embryonic stem cell-based therapy. Kennedy Institute of Ethics journal. 2012 Sep;22(3):243-61. PMID: 23285793.
68. Guan M, Xu Y, Wang W, Lin S. Differentiation into neurons of rat bone marrow-derived mesenchymal stem cells. European cytokine network. 2014 Jul-Sep;25(3):58-63. PMID: 25336204. DOI: 10.1684/ecn.2014.0357.
69. Zeng R, Wang LW, Hu ZB, Guo WT, Wei JS, Lin H, Sun X, Chen LX, Yang LJ. Differentiation of human bone marrow mesenchymal stem cells into neuron-like cells in vitro. Spine. 2011 Jun;36(13):997-1005. PMID: 21270716. DOI: 10.1097/BRS.0b013e3181eab764.
70. Cheng Z, Zheng Q, Wang W, Guo X, Wu Y, Zheng J. Targeted induction of differentiation of human bone mesenchymal stem cells into neuron-like cells. Journal of Huazhong University of Science and Technology Medical sciences = Hua zhong ke ji da xue xue bao Yi xue Ying De wen ban = Huazhong keji daxue xuebao Yixue Yingdewen ban. 2009 Jun;29(3):296-9. PMID: 19513609. DOI: 10.1007/s11596-009-0306-y.
71. Ni WF, Wu AM, Li QL, Huang ZY, Xu HZ, Yin LH. Induced human bone marrow stromal cells differentiate into neural cells by bFGF and cocultured with olfactory ensheathing cells. Current stem cell research & therapy. 2014;9(4):291-6. PMID: 24428604.
72. Vercelli A, Mereuta OM, Garbossa D, Muraca G, Mareschi K, Rustichelli D, Ferrero I, Mazzini L, Madon E, Fagioli F. Human mesenchymal stem cell transplantation extends survival, improves motor performance and decreases neuroinflammation in mouse model of amyotrophic lateral sclerosis. Neurobiology of disease. 2008 Sep;31(3):395-405. PMID: 18586098. DOI: 10.1016/j.nbd.2008.05.016.
73. Mazzini L, Mareschi K, Ferrero I, Miglioretti M, Stecco A, Servo S, Carriero A, Monaco F, Fagioli F. Mesenchymal stromal cell transplantation in amyotrophic lateral sclerosis: a long-term safety study. Cytotherapy. 2012 Jan;14(1):56-60. PMID: 21954839. DOI: 10.3109/14653249.2011.613929.
74. Salem AM, Ahmed HH, Atta HM, Ghazy MA, Aglan HA. Potential of bone marrow mesenchymal stem cells in management of Alzheimer's disease in female rats. Cell biology international. 2014 Dec;38(12):1367-83. PMID: 25044885. DOI: 10.1002/cbin.10331.
75. Lee JK, Jin HK, Bae JS. Bone marrow-derived mesenchymal stem cells reduce brain amyloid-beta deposition and accelerate the activation of microglia in an acutely induced Alzheimer's disease mouse model. Neuroscience letters. 2009 Jan 30;450(2):136-41. PMID: 19084047. DOI: 10.1016/j.neulet.2008.11.059.
76. Lee JK, Jin HK, Endo S, Schuchman EH, Carter JE, Bae JS. Intracerebral transplantation of bone marrow-

derived mesenchymal stem cells reduces amyloid-beta deposition and rescues memory deficits in Alzheimer's disease mice by modulation of immune responses. Stem cells (Dayton, Ohio). 2010 Feb;28(2):329-43. PMID: 20014009. DOI: 10.1002/stem.277.

77. Bae JS, Jin HK, Lee JK, Richardson JC, Carter JE. Bone marrow-derived mesenchymal stem cells contribute to the reduction of amyloid-beta deposits and the improvement of synaptic transmission in a mouse model of pre-dementia Alzheimer's disease. Current Alzheimer research. 2013 Jun;10(5):524-31. PMID: 23036020.

78. Hosseini M, Moghadas M, Edalatmanesh MA, Hashemzadeh MR. Xenotransplantation of human adipose derived mesenchymal stem cells in a rodent model of Huntington's disease: motor and non-motor outcomes. Neurological research. 2015 Apr;37(4):309-19. PMID: 25376132. DOI: 10.1179/1743132814y.0000000456.

79. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. Stem cells (Dayton, Ohio). 2010 Jun;28(6):1099-106. PMID: 20506226. DOI: 10.1002/stem.430.

80. Bao X, Wei J, Feng M, Lu S, Li G, Dou W, Ma W, Ma S, An Y, Qin C, Zhao RC, Wang R. Transplantation of human bone marrow-derived mesenchymal stem cells promotes behavioral recovery and endogenous neurogenesis after cerebral ischemia in rats. Brain research. 2011 Jan 7;1367:103-13. PMID: 20977892. DOI: 10.1016/j.brainres.2010.10.063.

81. Yoo SW, Kim SS, Lee SY, Lee HS, Kim HS, Lee YD, Suh-Kim H. Mesenchymal stem cells promote proliferation of endogenous neural stem cells and survival of newborn cells in a rat stroke model. Experimental & molecular medicine. 2008 Aug 31;40(4):387-97. PMID: 18779651. DOI: 10.3858/emm.2008.40.4.387.

82. Hsieh JY, Wang HW, Chang SJ, Liao KH, Lee IH, Lin WS, Wu CH, Lin WY, Cheng SM. Mesenchymal stem cells from human umbilical cord express preferentially secreted factors related to neuroprotection, neurogenesis, and angiogenesis. PloS one. 2013;8(8):e72604. PMID: 23991127. DOI: 10.1371/journal.pone.0072604.

83. Chen J, Li Y, Katakowski M, Chen X, Wang L, Lu D, Lu M, Gautam SC, Chopp M. Intravenous bone marrow stromal cell therapy reduces apoptosis and promotes endogenous cell proliferation after stroke in female rat. Journal of neuroscience research. 2003 Sep 15;73(6):778-86. PMID: 12949903. DOI: 10.1002/jnr.10691.

84. Joyce N, Annett G, Wirthlin L, Olson S, Bauer G, Nolta JA. Mesenchymal stem cells for the treatment of neurodegenerative disease. Regenerative medicine. 2010;5(6):933-46.

85. Olson SD, Pollock K, Kambal A, Cary W, Mitchell GM, Tempkin J, Stewart H, McGee J, Bauer G, Kim HS, Tempkin T, Wheelock V, Annett G, Dunbar G, Nolta JA. Genetically engineered mesenchymal stem cells as a proposed therapeutic for Huntington's disease. Molecular neurobiology. 2012 Feb;45(1):87-98. PMID: 22161544. DOI: 10.1007/s12035-011-8219-8.

86. Seo JH, Cho SR. Neurorestoration induced by mesenchymal stem cells: potential therapeutic mechanisms for clinical trials. Yonsei medical journal. 2012 Nov 1;53(6):1059-67. PMID: 23074102. DOI: 10.3349/ymj.2012.53.6.1059.

87. Sun H, Benardais K, Stanslowsky N, Thau-Habermann N, Hensel N, Huang D, Claus P, Dengler R, Stangel M, Petri S. Therapeutic potential of mesenchymal stromal cells and MSC conditioned medium in Amyotrophic Lateral Sclerosis (ALS)--in vitro evidence from primary motor neuron cultures, NSC-34 cells, astrocytes and microglia. PloS one. 2013;8(9):e72926. PMID: 24069165. DOI: 10.1371/journal.pone.0072926.

88. Uccelli A, Zappia E, Benvenuto F, Frassoni F, Mancardi G. Stem cells in inflammatory demyelinating disorders: a dual role for immunosuppression and neuroprotection. Expert opinion on biological therapy. 2006 Jan;6(1):17-22. PMID: 16370911. DOI: 10.1517/14712598.6.1.17.

89. Siatskas C, Payne NL, Short MA, Bernard CC. A consensus statement addressing mesenchymal stem cell transplantation for multiple sclerosis: it's time! Stem cell reviews. 2010 Dec;6(4):500-6. PMID: 20665128. DOI: 10.1007/s12015-010-9173-y.

90. Lu P, Jones LL, Snyder EY, Tuszynski MH. Neural stem cells constitutively secrete neurotrophic factors and promote extensive host axonal growth after spinal cord injury. Experimental neurology. 2003 Jun;181(2):115-29. PMID: 12781986.

91. Ibrahim Morales I, Toscano-Tejeida D, Ibarra A. Non Pharmacological Strategies to Promote Spinal Cord Regeneration: a View on Some Individual or Combined Approaches. Current pharmaceutical design. 2015 Dec 3. PMID: 26635267.

92. Bonner JF, Blesch A, Neuhuber B, Fischer I. Promoting directional axon growth from neural progenitors grafted into the injured spinal cord. Journal of neuroscience research. 2010 May 1;88(6):1182-92. PMID: 19908250. DOI: 10.1002/jnr.22288.

93. Aharonowiz M, Einstein O, Fainstein N, Lassmann H, Reubinoff B, Ben-Hur T. Neuroprotective effect of transplanted human embryonic stem cell-derived neural precursors in an animal model of multiple sclerosis. PloS one. 2008;3(9):e3145. PMID: 18773082. DOI: 10.1371/journal.pone.0003145.

94. Zhao LR, Piao CS, Murikinati SR, Gonzalez-Toledo ME. The role of stem cell factor and granulocyte-

colony stimulating factor in treatment of stroke. Recent patents on CNS drug discovery. 2013 Apr;8(1):2-12. PMID: 23173646.
95. Prakash A, Medhi B, Chopra K. Granulocyte colony stimulating factor (GCSF) improves memory and neurobehavior in an amyloid-beta induced experimental model of Alzheimer's disease. Pharmacology, biochemistry, and behavior. 2013 Sep;110:46-57. PMID: 23756182. DOI: 10.1016/j.pbb.2013.05.015.
96. Appel SH, Engelhardt JI, Henkel JS, Siklos L, Beers DR, Yen AA, Simpson EP, Luo Y, Carrum G, Heslop HE, Brenner MK, Popat U. Hematopoietic stem cell transplantation in patients with sporadic amyotrophic lateral sclerosis. Neurology. 2008 Oct 21;71(17):1326-34. PMID: 18936424. DOI: 10.1212/01.wnl.0000327668.43541.22.
97. Wyse RD, Dunbar GL, Rossignol J. Use of genetically modified mesenchymal stem cells to treat neurodegenerative diseases. International journal of molecular sciences. 2014;15(2):1719-45. PMID: 24463293. DOI: 10.3390/ijms15021719.
98. Huang B, Tabata Y, Gao JQ. Mesenchymal stem cells as therapeutic agents and potential targeted gene delivery vehicle for brain diseases. Journal of controlled release : official journal of the Controlled Release Society. 2012 Sep 10;162(2):464-73. PMID: 22885026. DOI: 10.1016/j.jconrel.2012.07.034.
99. van Velthoven CT, Kavelaars A, van Bel F, Heijnen CJ. Regeneration of the ischemic brain by engineered stem cells: fuelling endogenous repair processes. Brain research reviews. 2009 Jun;61(1):1-13. PMID: 19348860. DOI: 10.1016/j.brainresrev.2009.03.003.
100. Koh SH, Kim KS, Choi MR, Jung KH, Park KS, Chai YG, Roh W, Hwang SJ, Ko HJ, Huh YM, Kim HT, Kim SH. Implantation of human umbilical cord-derived mesenchymal stem cells as a neuroprotective therapy for ischemic stroke in rats. Brain research. 2008 Sep 10;1229:233-48. PMID: 18634757. DOI: 10.1016/j.brainres.2008.06.087.
101. Wakabayashi K, Nagai A, Sheikh AM, Shiota Y, Narantuya D, Watanabe T, Masuda J, Kobayashi S, Kim SU, Yamaguchi S. Transplantation of human mesenchymal stem cells promotes functional improvement and increased expression of neurotrophic factors in a rat focal cerebral ischemia model. Journal of neuroscience research. 2010 Apr;88(5):1017-25. PMID: 19885863. DOI: 10.1002/jnr.22279.
102. Kurozumi K, Nakamura K, Tamiya T, Kawano Y, Kobune M, Hirai S, Uchida H, Sasaki K, Ito Y, Kato K, Honmou O, Houkin K, Date I, Hamada H. BDNF gene-modified mesenchymal stem cells promote functional recovery and reduce infarct size in the rat middle cerebral artery occlusion model. Molecular therapy : the journal of the American Society of Gene Therapy. 2004 Feb;9(2):189-97. PMID: 14759803. DOI: 10.1016/j.ymthe.2003.10.012.
103. Kang SK, Lee DH, Bae YC, Kim HK, Baik SY, Jung JS. Improvement of neurological deficits by intracerebral transplantation of human adipose tissue-derived stromal cells after cerebral ischemia in rats. Experimental neurology. 2003 Oct;183(2):355-66. PMID: 14552877.
104. Nomura T, Honmou O, Harada K, Houkin K, Hamada H, Kocsis JD. I.V. infusion of brain-derived neurotrophic factor gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. Neuroscience. 2005;136(1):161-9. PMID: 16229956. DOI: 10.1016/j.neuroscience.2005.06.062.
105. Naderi-Meshkin H, Matin MM, Heirani-Tabasi A, Mirahmadi M, Irfan-Maqsood M, Edalatmanesh MA, Shahriyari M, Ahmadiankia N, Moussavi NS, Bidkhori HR, Bahrami AR. Injectable hydrogel delivery plus preconditioning of mesenchymal stem cells: exploitation of SDF-1/CXCR4 axis towards enhancing the efficacy of stem cells' homing. Cell biology international. 2015 Mar 31. PMID: 25825165. DOI: 10.1002/cbin.10474.
106. Naderi-Meshkin H, Bahrami AR, Bidkhori HR, Mirahmadi M, Ahmadiankia N. Strategies to improve homing of mesenchymal stem cells for greater efficacy in stem cell therapy. Cell biology international. 2015 Jan;39(1):23-34. PMID: 25231104. DOI: 10.1002/cbin.10378.
107. Sterneckert JL, Reinhardt P, Scholer HR. Investigating human disease using stem cell models. Nature reviews Genetics. 2014 Sep;15(9):625-39. PMID: 25069490. DOI: 10.1038/nrg3764.
108. Yu D, Silva GA. Stem cell sources and therapeutic approaches for central nervous system and neural retinal disorders. Neurosurgical focus. 2008;24(3-4):E11. PMID: 18341387. DOI: 10.3171/foc/2008/24/3-4/e10.
109. Balogh Z, Rethelyi J, Molnar M. [The role of induced pluripotent stem cells in modeling of neurological diseases]. Orvosi hetilap. 2015 Jun 28;156(26):1035-9. PMID: 26104665. DOI: 10.1556/650.2015.30179.
110. Niclis J, Trounson AO, Dottori M, Ellisdon A, Bottomley SP, Verlinsky Y, Cram D. Human embryonic stem cell models of Huntington disease. Reproductive biomedicine online. 2009 Jul;19(1):106-13. PMID: 19573298.
111. Ruiz-Lozano P, Rajan P. Stem cells as in vitro models of disease. Current stem cell research & therapy. 2007 Dec;2(4):280-92. PMID: 18220912.
112. Kefalopoulou Z, Aviles-Olmos I, Foltynie T. Critical aspects of clinical trial design for novel cell and gene therapies. Parkinson's disease. 2011;2011:804041. PMID: 22254150. DOI: 10.4061/2011/804041.
113. Mouhieddine TH, Kobeissy FH, Itani M, Nokkari A, Wang KK. Stem cells in neuroinjury and

neurodegenerative disorders: challenges and future neurotherapeutic prospects. Neural regeneration research. 2014 May 1;9(9):901-6. PMID: 25206908. DOI: 10.4103/1673-5374.133129.
114. Abrahamson EE, Ikonomovic MD, Dixon CE, DeKosky ST. Simvastatin therapy prevents brain trauma-induced increases in beta-amyloid peptide levels. Annals of neurology. 2009 Sep;66(3):407-14. PMID: 19798641. DOI: 10.1002/ana.21731.
115. Scherzinger E, Lurz R, Turmaine M, Mangiarini L, Hollenbach B, Hasenbank R, Bates GP, Davies SW, Lehrach H, Wanker EE. Huntingtin-encoded polyglutamine expansions form amyloid-like protein aggregates in vitro and in vivo. Cell. 1997 Aug 8;90(3):549-58. PMID: 9267034.
116. Tran PB, Miller RJ. Aggregates in neurodegenerative disease: crowds and power? Trends in neurosciences. 1999 May;22(5):194-7. PMID: 10322490.
117. Mueller-Steiner S, Zhou Y, Arai H, Roberson ED, Sun B, Chen J, Wang X, Yu G, Esposito L, Mucke L, Gan L. Antiamyloidogenic and neuroprotective functions of cathepsin B: implications for Alzheimer's disease. Neuron. 2006 Sep 21;51(6):703-14. PMID: 16982417. DOI: 10.1016/j.neuron.2006.07.027.
118. Grondin R, Zhang Z, Yi A, Cass WA, Maswood N, Andersen AH, Elsberry DD, Klein MC, Gerhardt GA, Gash DM. Chronic, controlled GDNF infusion promotes structural and functional recovery in advanced parkinsonian monkeys. Brain : a journal of neurology. 2002 Oct;125(Pt 10):2191-201. PMID: 12244077.
119. Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics. 2005 Jan;2(1):3-14. PMID: 15717053. DOI: 10.1602/neurorx.2.1.3.
120. Upadhyay RK. Drug delivery systems, CNS protection, and the blood brain barrier. BioMed research international. 2014;2014:869269. PMID: 25136634. DOI: 10.1155/2014/869269.
121. Barua NU, Woolley M, Bienemann AS, Johnson DE, Lewis O, Wyatt MJ, Irving C, O'Sullivan S, Murray G, Fennelly C, Skinner P, Gill SS. Intermittent convection-enhanced delivery to the brain through a novel transcutaneous bone-anchored port. Journal of neuroscience methods. 2013 Apr 15;214(2):223-32. PMID: 23419699. DOI: 10.1016/j.jneumeth.2013.02.007.
122. Mandel RJ, Snyder RO, Leff SE. Recombinant adeno-associated viral vector-mediated glial cell line-derived neurotrophic factor gene transfer protects nigral dopamine neurons after onset of progressive degeneration in a rat model of Parkinson's disease. Experimental neurology. 1999 Nov;160(1):205-14. PMID: 10630205. DOI: 10.1006/exnr.1999.7203.
123. Lindvall O, Wahlberg LU. Encapsulated cell biodelivery of GDNF: a novel clinical strategy for neuroprotection and neuroregeneration in Parkinson's disease? Experimental neurology. 2008 Jan;209(1):82-8. PMID: 17963752. DOI: 10.1016/j.expneurol.2007.08.019.
124. Sajadi A, Bensadoun JC, Schneider BL, Lo Bianco C, Aebischer P. Transient striatal delivery of GDNF via encapsulated cells leads to sustained behavioral improvement in a bilateral model of Parkinson disease. Neurobiology of disease. 2006 Apr;22(1):119-29. PMID: 16300956. DOI: 10.1016/j.nbd.2005.10.006.
125. Klein SM, Behrstock S, McHugh J, Hoffmann K, Wallace K, Suzuki M, Aebischer P, Svendsen CN. GDNF delivery using human neural progenitor cells in a rat model of ALS. Human gene therapy. 2005 Apr;16(4):509-21. PMID: 15871682. DOI: 10.1089/hum.2005.16.509.
126. Suzuki M, McHugh J, Tork C, Shelley B, Klein SM, Aebischer P, Svendsen CN. GDNF secreting human neural progenitor cells protect dying motor neurons, but not their projection to muscle, in a rat model of familial ALS. PloS one. 2007;2(8):e689. PMID: 17668067. DOI: 10.1371/journal.pone.0000689.
127. Hoban DB, Howard L, Dowd E. GDNF-secreting mesenchymal stem cells provide localized neuroprotection in an inflammation-driven rat model of Parkinson's disease. Neuroscience. 2015 Sep 10;303:402-11. PMID: 26166730. DOI: 10.1016/j.neuroscience.2015.07.014.
128. Lee HJ, Kim KS, Kim EJ, Choi HB, Lee KH, Park IH, Ko Y, Jeong SW, Kim SU. Brain transplantation of immortalized human neural stem cells promotes functional recovery in mouse intracerebral hemorrhage stroke model. Stem cells (Dayton, Ohio). 2007 May;25(5):1204-12. PMID: 17218400. DOI: 10.1634/stemcells.2006-0409.
129. Niu M, Hammond P, 2nd, Coger RN. The effectiveness of a novel cartridge-based bioreactor design in supporting liver cells. Tissue engineering Part A. 2009 Oct;15(10):2903-16. PMID: 19271993. DOI: 10.1089/ten.TEA.2008.0279.
130. Zhu ZH, Qiu YD, Shi XL, Xie T, Ding YT. [Construction of a novel bioreactor of bioartificial liver system with human bone marrow mesenchymal stem cells]. Zhongguo wei zhong bing ji jiu yi xue = Chinese critical care medicine = Zhongguo weizhongbing jijiuyixue. 2010 Dec;22(12):719-22. PMID: 21190596.