

Stem Cell Challenges in the Treatment of Neurodegenerative Disease

Zhongling Feng¹ & Feng Gao²

¹ Bio Group, Nitto Denko Technical Corporation, Oceanside, CA, USA

² Wintherix, LLC, San Diego, CA, USA

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Correspondence

Zhongling Feng, MD, Ph.D, Bio Group, Nitto Denko Technical Corporation

Oceanside, CA 92058, USA.

Tel.: 1-858-534-2713;

Fax: 1-760-435-7050;

Email: Zhongling_feng@gg.nitto.co.jp

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SUMMARY

Neurodegenerative diseases result from the gradual and progressive loss of neural cells and lead to nervous system dysfunction. The rapidly advancing stem cell field is providing attractive alternative options for fighting these diseases. Results have provided proof of principle that cell replacement can work in humans with Parkinson's disease (PD). However, three clinical studies of cell transplantation were published that found no net benefit, while patients in two of the studies developed dyskinesias that persisted despite reductions in treatment. Induced pluripotent stem cells (iPSC) have major potential advantages because patient-specific neuroblasts are suitable for transplantation, avoid immune reactions, and can be produced without the use of human ES cells (hESC). Although iPSCs have not been successfully used in clinical trials for PD, patients with amyotrophic lateral sclerosis (ALS) were treated with autologous stem cells and, though they had some degree of decline one year after treatment, they were still improved compared with the preoperative period or without any drug therapy. In addition, neural stem cells (NSCs), via brain-derived neurotrophic factor (BDNF), have been shown to ameliorate complex behavioral deficits associated with widespread Alzheimer's disease (AD) pathology in a transgenic mouse model of AD. So far, the FDA lists 18 clinical trials treating multiple sclerosis (MS), but most are in preliminary stages. This article serves as an overview of recent studies in stem cell and regenerative approaches to the above chronic neurodegenerative disorders. There are still many obstacles to the use of stem cells as a cure for neurodegenerative disease, especially because we still don't fully understand the true mechanisms of these diseases. However, there is hope in the potential of stem cells to help us learn and understand a great deal more about the mechanisms underlying these devastating neurodegenerative diseases.

Introduction

Neurodegenerative diseases result from the gradual and progressive loss of neural cells, leading to nervous system dysfunction [1].

The hallmark of several degenerative disorders in the central nervous system (CNS), such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), multiple sclerosis (MS), and Alzheimer's disease (AD), is the massive loss of one or several types of neurons. The nerve path was first thought to be static, immobile, and incapable of regeneration. However, much evidence demonstrates that generation of new neurons, namely neurogenesis, is not entirely restricted to prenatal development, but continues throughout adult life in certain regions of the mammalian brain [2]. A number of stem and progenitor cell types have been proposed as therapy for neurological disease ranging from neural stem cells (NSCs) to bone marrow-derived stem cells to embryonic stem cells (ESC). All of these have been grafted into a rat parkinsonian ani-

mal model where they survive, differentiate into neurons and glial cells, express tyrosine hydroxylase, and ameliorate neurological deficits. Despite these successes, the most immediate impact on patients will be achieved by making use of the trophic support capability of cell therapy and not by a cell replacement mechanism [3].

Stem cell therapy and cell regenerative approaches to neurological diseases can be divided into a number of categories depending upon the target neurological disease. These diseases include those caused by acute injury, chronic neurodegenerative disorders, chronic inflammatory and immunologically mediated conditions, and genetic diseases that present in childhood. Proposed stem cell and regenerative approaches to these diseases have been extensively reviewed in many articles [4–7].

One of the reasons for failure of neuroprotective treatments in an acute injury has been the need to start treatment early. In the case of stroke, treatment is required within 3–6 hours of the onset of ischemia, which has proven difficult in clinical practice [3].

Based on this fact, stem cell therapy is more practicable for chronic conditions. In this review, stem cell and regenerative approaches will be discussed as they relate to the chronic neurodegenerative disorders.

Stem Cells and Parkinson's Disease

The main pathology underlying motor symptoms in PD is a progressive degeneration of mesencephalic dopaminergic (DA) neurons projecting to the striatum, but nondopaminergic systems, for example, in the lower brain stem and cortical areas, can also be affected. Current therapeutic options for PD patients include L-dopa, dopamine agonists, enzyme inhibitors and deep brain stimulation in the thalamus, subthalamic nucleus, and globus pallidus [8–10]. So far, pharmacological dopamine replacement is only a symptomatic therapy and can cause significant side effects with long-term use, including drug-induced motor complications such as “on–off” fluctuations and levodopa-induced dyskinesias. The major challenge in PD is to find a strategy to prevent it or to slow down its progression after it has started.

The rapidly advancing stem cell field is providing attractive alternative options for fighting this disease. Of these, ESC and induced pluripotent stem cells (iPSC) seem to be most promising. The principal goals for any stem cell-based cell replacement therapy in PD include the development of xenogenic-free culture protocols that can generate large numbers of relatively defined transplantable cells, adequate survival and functional efficacy from the grafted cells following transplantation, and the avoidance of potential adverse effects of stem cell-derived grafts—such as tumor formation and immune rejection. The cell sources include mesenchymal stem cells (MSCs) [11,12], ESCs [8], and iPSC [13–17].

A suitable autologous cell source for cellular therapy is an ideal strategy in PD patients. Bone marrow contains a heterogeneous population of cells and notably contains at least two stem cell populations: hematopoietic stem cells and MSCs. Barzilay et al. induced DA neuron differentiation of bone marrow MSCs via forced expression of *LMX1a*. Combining MSCs and lentiviral gene delivery technology, they have shown that gene manipulation of adult MSCs may help to facilitate DA cell differentiation. Following lentiviral transduction of MSCs with *MX1a* they observed a transcriptional profile characteristic of a developing mesodiencephalic neuron, even though the cells originated from an adult donor [18].

After many encouraging open-label studies of fetal cell transplantation for PD from 2001 to 2003, three prospective, randomized, double-blind, placebo-controlled studies of cell transplantation were published and found no net benefit. In addition, patients in two of the studies developed dyskinesias that persisted despite reductions in treatment. Theoretically, the stem cell-derived cells should release dopamine in a regulated manner, and exhibit the molecular, morphological, and electrophysiological properties of substantia nigra neurons. In animal models, they do show the ability to reverse motor deficits resembling the symptoms in human patients; they reestablish a dense terminal network throughout the striatum, and become functionally integrated into host neural circuitries [10]. To realize the potential of stem cells, research has been undertaken to understand and overcome the dual problems of an unpredictable benefit and troublesome dyskinesias after DA

cell transplantation. There is an ongoing debate about the genesis of the graft-induced persistent dyskinesias in the double-blind studies. It is suggested that, given enough time, the host brain may induce a PD phenotype on transplanted neurons. If that is the case, not only may cell transplantation be inappropriate for PD, but the search for the etiology of PD may now need to focus on other tissues besides DA neurons [19].

One of the most exciting recent developments is the demonstration that somatic cells can be reprogrammed to a pluripotent state. The major potential advantage of this approach is that patient-specific DA neuroblasts suitable for transplantation, which avoid immune reactions, can be produced without the use of human ES cells (hESC). However, it has been demonstrated in the mouse system that iPSC-derived chimeras frequently develop tumors resulting from reactivation of the oncogene *c-Myc*. Soldner et al. [20] established human induced pluripotent stem cell (hiPSC) lines from five patients with idiopathic PD using doxycycline (DOX)-inducible lentiviral vectors transducing either three or four reprogramming factors. These cells were shown to have all of the features of pluripotent hESCs, including the ability to differentiate into cell types of all embryonic lineages. They showed that fibroblasts from five patients with sporadic PD could be efficiently reprogrammed and demonstrated that these patient-derived hiPSCs could be subsequently differentiated *in vitro* into DA neurons. Moreover, using DOX-inducible lentiviral vectors that could be excised with Cre-recombinase, they generated hiPSCs that are free of the reprogramming factors. These factor-free hiPSCs maintained all of the characteristics of a pluripotent ESC-like state after removal of the transgenes. Importantly, genome-wide transcription analysis revealed that residual transgene expression from the partially silenced viral vectors did in fact perturb overall gene expression in hiPSCs, such that the factor-free hiPSCs more closely resembled embryo-derived hESCs than the parental virus-carrying hiPSCs. The results described so far showed that DOX-inducible delivery of the reprogramming factors can efficiently generate hiPSCs from skin biopsies obtained from PD patients in the absence of *c-MYC* with similar kinetics and efficiencies.

Much work still remains to determine the survival, growth capacity, and functionality of the DA neurons generated from iPSCs, however, the use of the patient's own cells might be associated with increased susceptibility to the degenerative process in PD. Better criteria for selecting the most suitable patients with respect to stage and type of PD have to be defined, and the preoperative degeneration pattern has to be determined using imaging techniques such as positron emission tomography (PET). With respect to the dose and site of implantation of DA cells, the transplantation procedure needs to be tailor-made on the basis of preoperative imaging so that the repair of the DA system is as complete as possible in each patient's brain.

Another hurdle for cellular therapy is how to track the engrafted cells *in vivo* after cell transplantation. Magnetic resonance imaging (MRI) of magnetically labeled stem cells has become a valuable noninvasive cell tracking tool in the understanding and evaluation of experimental stem cell-based therapies of degenerative CNS disorders. A study from Stroh et al. strongly suggested that molecular MRI approaches may be beneficial but must be carefully tailored to the respective cell population in order to exert minimal physiologic impact and ensure the feasibility of this imaging approach for

clinical applications [21]. The risk of tumor formation when the grafted DA neurons have been derived from iPSCs and the consequences of the introduction of new genes in stem cell-derived neurons should be carefully evaluated after transplantation in animal models before clinical application.

So far, 300–400 patients with PD have been grafted with human embryonic mesencephalic tissue. The results from these patients have provided proof of principle that cell replacement can work in the human PD brain. Cell-therapy research in PD is now entering its second phase and the main objective is to develop this approach into a clinically useful treatment. Evidence shows that the underlying disease process does not destroy the transplanted fetal DA cells [22,23], however, if the patient's original DA system continues to degenerate, and if diseased cells still excrete toxic factors, the engrafted cells may be killed. Whether PD pathological processes are influencing the grafted neurons should be carefully considered.

On the contrary, Madhavan et al. reported stimulation of endogenous cells after transplantation. They studied whether Neural Progenitor Cells (NPCs), when transplanted prior to the toxic insult, could stimulate endogenous NPCs and induce neuroprotection in a parkinsonian rat model. They hypothesized that there exists a synergism between the actions of endogenous and grafted NPCs after transplantation that would lead to neuroprotection in a 6-OHDA rat model of PD [24]. Their data indicated that NPC implantation prior to a toxic insult can stimulate significant endogenous NPC proliferation, migration, and neuronal differentiation associated with nigrostriatal protection. The data also suggested that, in their model, graft-expressed Glial cell-derived neurotrophic factor (GDNF), Sonic hedgehog (Shh), and stromal cell-derived factor 1 alpha (SDF1- α), may play a role in initiating the endogenous NPC response and lead to neuroprotection.

The above-mentioned phenomenon of so-called "transplantation-induced neurogenesis" may be explained by grafted NPCs acting as biological mini-pumps for release of growth factors and chemokines that stimulate plastic responses from the host, including the stimulation of endogenous neurogenesis. Investigating the molecular basis of such communication between these two NPC types may help develop optimal cell therapies for PD [24].

There is yet limited understanding of optimal cell transfer parameters and patient selection. For the patients who have received cell transplants in Sweden, Canada, and the United States, it is not clear why some transplants work whereas others do not [25]. What has now become clear is that no procedure to date has induced reliable neurogenesis in the substantia nigra of the adult rat or monkey [25].

Further development and optimization of the safety and efficacy of the techniques involved in generating and manipulating these, as well as other cell sources, will be essential before any further clinical trials are carried out [8]. Such efforts also require information about optimal surgical and procedural applications, including cell implantation locations, cell dosage, cell preparations, trophic factors, and immunological and connectivity variables to allow functional reconstitution of neurocircuitry. So far, no scientifically based clinical trials with stem cell therapy have been performed in PD patients, and the future potential of cell replacement therapy in PD is still unclear.

Stem Cells and ALS

ALS, also known as Lou Gehrig's disease, is a devastating neurodegenerative disorder, and only minimally effective therapy exists. Around 1 in 400 individuals die of the condition worldwide [26,27].

In recent animal model studies of lysosomal storage diseases and leukodystrophy, hematopoietic stem cell transplantation has been associated with suppression of neuroinflammation after engraftment of donor-derived cells at sites of injury. The beneficial effect of suppressing inflammation and prolonging survival in a mutant Cu²⁺/Zn²⁺ superoxide dismutase (mSOD1) mouse model [28,29] prompted the study to determine whether allogeneic human hematopoietic stem cells could engraft at sites of injury within the spinal cord and improve clinical outcomes of ALS.

A study from Appel et al. demonstrated that peripheral cells derived from donor hematopoietic stem cells can enter the human CNS primarily at sites of motoneuron pathology and engraft as immunomodulatory cells. Although unmodified hematopoietic stem cells did not benefit these sporadic ALS patients, such cells may provide a cellular vehicle for future CNS gene therapy [27].

Eggan's group also demonstrated the feasibility of producing large numbers of motor neurons with a patient's exact genotype, which would be immune matched to that individual—a long sought-after goal of regenerative medicine. However, they comment that several major challenges must be resolved before cell replacement therapy using iPSC technology can become a clinical reality. First, among several other safety issues, iPSC-derived neurons will not be suitable for transplantation until the oncogenes and retroviruses used are replaced with more controlled methods of reprogramming. Second, it will likely be necessary to understand and correct any intrinsic defects in the patient's neurons and glia before they can be used to generate iPSCs for cell therapy [30,31].

A major challenge has been delivering MSCs efficiently to a target tissue, such as skeletal muscle, for optimal cell survival, migration, and incorporation. Suzuki and colleagues have partly overcome this problem by optimizing the engraftment of the cells. The most exciting part of Suzuki's work highlighted that neurotrophic factors such as GDNF are effective in sparing motor neuron death and increasing survival in a very rapidly progressing animal model of ALS, bringing neurotrophic factors back into the spotlight for this disease. [32,33]

Several reports about the autologous transplantation of stem cells from bone marrow to ALS patients have been reported outside of the United States. These results showed that stem cell therapy is a safe and effective treatment for ALS patients. The patients had some degree of decline 1 year after stem cell therapy but they were still improved compared with the preoperative period, or without any drug therapy for ALS. However, further studies with a greater number of patients are necessary to define the usefulness of stem-cell therapy in patients with confirmed ALS [34,35].

Strategies used to develop stem cell-based therapies for ALS are also summarized in Feldman's work. He states that further progress will depend upon the development of new stem cell lines to expand our understanding of the therapeutic capabilities of stem cells in ALS. While stem cells alone could replace lost

motor neurons or provide benefits via astrocyte or glial replacement, overwhelming evidence suggests that neurotrophic support has a major impact on motor neuron survival and function. Further evidence suggests that stem cells are capable of secreting growth factors, and may in fact slow disease progression in ALS models through the combined effects of neuron replacement and paracrine growth factor production. A promising approach to the treatment of ALS is to harness both of these beneficial effects by implanting stem cells selected or engineered to deliver optimal growth factor support. Finally, the fact that motor neuron cell bodies and axon terminals are located in separate microenvironments must be considered. A successful comprehensive therapeutic approach to maintaining motor neuron survival and function will likely require tailored trophic support at multiple sites along the neural pathway [36].

Stem Cells and Alzheimer's Disease

Stem cell replacement—including neural stem cell replacement—therapeutic potential for AD has been extensively reviewed before [37–40].

In AD, cognitive dysfunction correlates best not with Amyloid-beta ($A\beta$) or tau pathology, but rather with hippocampal synaptic density. Growing evidence also suggests that soluble $A\beta$ oligomers impair cognition and long-term potentiation by binding to synapses and altering synaptic shape, composition, and density. Very few treatments restore cognition in AD models without attenuating at least one of these pathologies. NSCs might compensate for the toxic effects of oligomers on synaptic connectivity.

Although stem cells have been suggested as a potential therapy for AD, this approach has not yet been directly tested in transgenic AD models. To determine whether brain-derived neurotrophic factor (BDNF) is required for NSC-induced cognitive rescue, Mathew Blurton-Jones et al. used lentiviral delivery of shRNA to stably knockdown BDNF expression in NSCs and then transplanted wild type and BDNF knockdown cells into 3xTg-AD mice—a model that recapitulates many of the salient features of AD. Interestingly, despite widespread and established $A\beta$ plaque and neurofibrillary tangle pathology, hippocampal transplantation of wild-type NSCs, but not BDNF knockdown NSCs, rescued the spatial learning and memory deficits in aged 3xTg-AD mice. Western blot analysis confirmed these findings, revealing a 45% increase in synaptophysin protein levels in NSC-injected mice. This difference provides a structural basis for the observed improvement in cognition in large part by elevating BDNF expression and increased synaptic density in the NSC-injected 3xTg-AD mice, and clearly demonstrates that NSCs can ameliorate complex behavioral deficits associated with widespread AD pathology via BDNF (a bystander-like mechanism) [41].

Recently, Porayette et al. [42] reported the functional role of $A\beta$ precursor protein ($A\beta$ PP) and its cleavage products during early embryonic neurogenesis. They examined the expression and processing of this protein and its role in proliferation and differentiation of hESCs into neural precursor cells (NPCs). They found that amyloidogenic processing of $A\beta$ PP promotes hESC proliferation whereas nonamyloidogenic processing induces hESC differentiation into NPCs. Their data revealed that the early expression and

differential processing of $A\beta$ PP are normal processes important for early embryonic neurogenesis. Subtle changes in the processing of $A\beta$ PP by neuronal cells and/or resident NSCs in the adult during aging may underlie the cell cycle changes and apoptotic cell death observed in AD. These data indicate hESCs as a useful model for understanding both neurogenesis and neurodegeneration. Finally these results have important implications for current therapeutic strategies aimed at modulating $A\beta$ production as well as stem cell replacement therapies for treating neurodegenerative diseases.

Stem Cells and MS

MS is a chronic inflammatory, demyelinating, neurodegenerative disease of the CNS, characterized by patchy perivenular inflammatory infiltrates in areas of demyelination and axonal loss [43,44]. There are currently no means to improve oligodendrocyte recovery and myelin regeneration, but stem cell-based regenerative medicine raises great hope for the treatment of MS.

Myelin regeneration can be improved either by cell replacement therapy, as a substitute to the endogenous pool of oligodendrocyte progenitor cells (OPCs), or by boosting the brain's intrinsic capacity for remyelination. While NPCs have promising remyelinating potential, recent studies have suggested that they may also secrete neurotrophic factors. Einstein and Ben-Hur hypothesized that NPC transplantation may enhance the myelin regeneration capabilities of host brain cells. To this end they used the model of chronic cuprizone exposure that produces extensive demyelination in aged mice, in which the rate of remyelination is slow. They showed that intracerebroventricular (ICV) NPC transplantation induced a notable improvement in remyelination in cuprizone-treated mice. The enhanced remyelination was attributed solely to endogenous cells. ICV-transplanted NPCs facilitated host brain OPC proliferation, an effect mediated by platelet-derived growth factor (PDGF)-AA and fibroblast growth factor (FGF)-2. These results suggested that transplanted NPCs exert trophic effects on their environment to enhance remyelination by the host brain pool of progenitor cells [44].

The capacity of cells to home in damaged sites in the CNS is a crucial aspect when attempting to employ cell therapy in MS due to the multifocal nature of the disease. MSCs are known for their migratory properties owing to their eclectic expression of chemokine receptors and ligands. The neurotrophic factor-producing cell (NTFC) traits (migration and neurotrophic factor secretion capacity) also imply that the paracrine function of the cells mediates the clinical improvement observed in the mice described in a study by Barhum et al.; either through immunomodulation, neuroprotection, or possibly other cell–cell interactions. These results may lay the foundation for possible autologous stem cell regenerative therapy for MS patients in the future [45].

BDNF, a member of the neurotrophin family, is neuroprotective in animal models of neurodegenerative diseases. However, BDNF has a short half-life and its efficacy in the CNS, when delivered peripherally, is limited due to the blood–brain barrier. Makar et al. [46] have developed a means of delivering BDNF into the CNS using genetically engineered bone marrow stem cells (BMSCs) as a vehicle, and have explored the clinical effects of BDNF on outcomes in experimental autoimmune encephalomyelitis (EAE),

an animal model of MS. BDNF-engineered-BMSCs were transplanted (i.v.) into irradiated 2-week-old SJL/J female mice. Eight weeks after transplantation, mice were immunized with a peptide of proteolipid protein (PLP139–151), to induce EAE. Mice that had received BDNF-engineered-BMSCs showed a significant delay in EAE onset and a reduction in overall clinical severity compared to mice receiving BMSC transfected with an empty vector lacking the BDNF gene. In addition, pathological examination showed that BDNF delivery reduced demyelination and increased remyelination. Inhibition of proinflammatory cytokines TNF- α and IFN- γ and enhanced expression of the anti-inflammatory cytokines IL-4, IL-10, and IL-11 were found in the CNS tissues of the BDNF transplanted group. These results support the use of BMSCs as vehicles to deliver BDNF into the CNS of EAE animals. This is a potentially novel therapeutic approach that might be used to deliver BDNF gene or genes of other therapeutic proteins into the CNS in MS or in other diseases of the CNS in which accessibility of therapeutic proteins is limited due to the blood–brain barrier.

So far, the FDA lists 18 clinical trials treating MS (Table 1). Several have been completed, but most of them have yet to recruit patients, so it is hard to review these clinical trials. The translation of stem cell research to human trials must constitute the ultimate goal.

Conclusion

Neurodegenerative disorders have always been an attractive target for cell therapy and tissue transplantation. However, it has proven to be more difficult to treat than expected. For example, PD involves more than dopaminergic degeneration in the substantia nigra, meaning that more than mesencephalic transplantation will be needed. Side effects, such as the dyskinesias reported in two randomized, controlled studies, are also a significant problem [47,48].

If we cannot replace damaged cells or create new neurons, can we provide the environment for damaged cells to recover? C Boucherie et al. [49] have extensively reviewed several observations that support the hypothesis that stem cells may have a valuable influence on diseased host tissues by exerting a protective “chaperone” effect.

Another concern of transplanting such undifferentiated cells is the possible formation of teratomas [50]. Furthermore, stem cells and cancer are inextricably linked [51]. After transplantation, are there signals to direct the stem cells’ differentiation and subsequent migration to the correct niche, or are there niches that attract these implanted stem cells and then cause them to proliferate and differentiate? If their growth cannot be controlled, they may form a tumor, which may cause more damage than the original disease. Even if they differentiate, would these cells have the intended function, or any function at all? In order to answer these questions, more understanding is needed about the intrinsic and extrinsic mechanisms that control the various steps of neurogenesis, including proliferation, survival, fate specification, migration, maturation, and synapse formation. How to keep self-renewal under control and avoid immortalization and transformation still remains to be discovered. Four very promising approaches to making stem cell-based regenerative medicine safer have been proposed: transplants of progenitors rather than pluripotent stem cells, in-

roduction of a stem cell-specific suicide gene, directed removal of residual stem cells based on a nongenetic method, and the use of stem cells themselves for transplantation after elimination of their tumor forming potential without genetic modification. These approaches should enhance the safety of any regenerative medicine therapy [50].

From conventional drugs to gene therapy [52–55], many hopeful treatments arise, but each is soon eliminated. There are still many obstacles to the use of stem cells as a cure for neurodegenerative disease, especially because we still don’t fully know and understand the real mechanisms of these diseases. Cell replacement has only occurred in a black box, and we must rely solely on the recovery of brain function to determine whether it was effective, but cannot determine a mechanistic explanation for the recovery. In addition, if the engrafted cells are derived from diseased cells, we may doubt the long-term effectiveness of these cells, due to the possibility that they may contain genes or proteins associated with disease.

Stem cells do provide hope, however, because we might be able to understand more about the pathogenesis of these diseases through patient-derived stem cells. It may also be possible to combine gene therapy and stem cell transplantation by using stem cells as a vehicle [56,57]. Recently, Thomas Vierbuchen et al. [58] identified a combination of only three factors—Ascl1, Brn2 (also called Pou3f2) and Myt1l—which are sufficient to rapidly and efficiently convert mouse embryonic and postnatal fibroblasts into functional neurons *in vitro*. These induced neuronal (iN) cells express multiple neuron-specific proteins, generate action potentials, and form functional synapses. Generation of iN cells from nonneural lineages could have important implications for studies of neural development, neurological disease modeling, and regenerative medicine.

Optimal cell transfer parameters and patient selection for neurodegenerative diseases should be established globally. Such efforts also require information about optimal surgical and procedural applications, including cell implantation locations, cell dosage, cell preparations, trophic factors, and immunological and connectivity variables to allow functional reconstitution of neurocircuitry. In addition, further studies with a greater number of patients are necessary to define the usefulness of stem-cell therapy in patients with neurodegenerative diseases. The ultimate goal must remain the translation of stem cell research to human trials, and effective clinical treatments.

The road is paved, but we don’t know whether it goes the right direction. There is hope in the potential of stem cells to help us learn and understand a great deal more about the mechanisms underlying these devastating neurodegenerative diseases, but there is much work to be done to reach the ultimate goal of a cure.

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Conflict of Interest

The authors state that they have no conflict of interest pertaining to this manuscript.

Table 1 Proposed and completed clinical trials registered in the FDA database

Rank	Status	Study	Intervention
1	Recruiting	Stem cell therapy for patients with multiple sclerosis failing interferon a randomized study	Procedure: hematopoietic stem cell therapy
2	Active, not recruiting	Hematopoietic stem cell therapy for patients with multiple sclerosis	Procedure: hematopoietic stem cell transplantation
3	Active, not recruiting	Donor stem cell transplantation for the treatment of multiple sclerosis	Procedure: stem cell transplant
4	Active, not recruiting	High-dose immunosuppression and autologous transplantation for multiple sclerosis (HALT MS) study	Drug: granulocyte-colony stimulating factor (G-CSF) and prednisone; Drug: carmustine, etoposide, cytarabine, and melphalan (BEAM); Procedure: autologous hematopoietic stem cell transplant
5	Recruiting	Autologous mesenchymal stem cells from adipose tissue in patients with secondary progressive multiple sclerosis	Other: autologous mesenchymal stem cells from adipose tissue
6	Active, not recruiting	Mesenchymal stem cells in multiple sclerosis (MSCIMS)	Procedure: MSC treatment
7	Active, not recruiting	Mesenchymal stem cells for the treatment of MS	Biological: injection of autologous stem cells
8	Completed	Immunological mechanisms of hematopoietic stem cell transplantation in multiple sclerosis	Procedure: stem cell transplantation
9	Completed	High dose chemo/radiotherapy and hematopoietic stem cell transplant for patients with multiple sclerosis	Drug: cyclophosphamide; Drug: ATG; drug: MESNA; Procedure: radiation therapy
10	Not yet recruiting	Rajavithi neuronal adult stem cells project	Other: progenitor stem cell culture
11	Not yet recruiting	Autologous mesenchymal stem cell (MSC) transplantation in MS	Biological: autologous mesenchymal stem cell transplantation
12	Completed	Phase I study of high-dose cyclophosphamide and total body irradiation with T lymphocyte-depleted autologous peripheral blood stem cell or bone marrow rescue in patients with multiple sclerosis	Drug: cyclophosphamide; Drug: filgrastim; Drug: methylprednisolone; Procedure: autologous stem cell transplantation
13	Completed	Phase I pilot study of total-body irradiation, anti-thymocyte globulin and cyclophosphamide followed by syngeneic or autologous peripheral blood stem cell transplantation in patients with multiple sclerosis	Drug: anti-thymocyte globulin; Drug: cyclophosphamide; Drug: filgrastim; Drug: prednisone; Procedure: peripheral blood stem cell transplantation; Procedure: irradiation
14	Recruiting	Nonmyeloablative allo stem cell transplant for severe autoimmune diseases	Procedure: nonmyeloablative allogeneic stem cell transplant
15	Recruiting	Oligodendrocyte progenitor cell culture from human brain	Procedure: oligodendrocyte progenitor cell culture/craniotomy
16	Recruiting	Scleroderma: cyclophosphamide or transplantation (SCOT)	Procedure: autologous stem cell transplantation and high-dose immunosuppressive therapy (HDIT); Drug: cyclophosphamide; Drug: equine antithymocyte drug: methylprednisolone; Drug: growth colony stimulating factor (G-CSF); Radiation: total body irradiation (TBI)
17	Recruiting	Allogeneic mesenchymal stem cells transplantation for systemic sclerosis (SSc)	Biological: allogeneic mesenchymal stem cells (AlloMSC)
18	Active, not recruiting	Development of iPS from donated somatic cells of patients with neurological diseases	

Adapted from <http://clinicaltrials.gov/ct2/results?term=Stem+Cell+Therapy+%26+Multiple+Sclerosis>.

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