



Published in final edited form as:

Brain Res. 2016 May 1; 1638(Pt A): 88–96. doi:10.1016/j.brainres.2015.06.053.

Regenerative Cellular Therapies for Neurologic Diseases

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Abstract

The promise of stem cell regeneration has been the hope of many neurologic patients with permanent damage to the central nervous system. There are hundreds of stem cell trials worldwide intending to test the regenerative capacity of stem cells in various neurological conditions from Parkinson's disease to multiple sclerosis. Although no stem cell therapy is clinically approved for use in any human disease indication, patients are seeking out trials and asking clinicians for guidance. This review summarizes the current state of regenerative stem cell transplantation divided into seven conditions for which trials are currently active: demyelinating diseases/spinal cord injury, amyotrophic lateral sclerosis, stroke, Parkinson's disease, Huntington's disease, macular degeneration and peripheral nerve diseases.

Keywords

stem cells; regeneration; neurologic diseases

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Disclosures and Contributions:

Dr. Levy receives research support from NIH, Guthy Jackson Charitable Foundation, Acorda, Sanofi, NeuralStem and Genentech, and serves as a consultant for Chugai Pharmaceuticals, Glaxo-Smith-Kline, Medimmune. Dr. Levy's contribution to the manuscript was to write the introduction, stem cell types and demyelinating disease sections and to critically revise the manuscript.

Dr. Boulis receives research support from NIH, NeuralStem, the Cox Foundation, the Virginia Gentleman's Foundation, Department of Defense, Taubman Foundation and served as a consultant for NeuralStem. Dr. Boulis's contribution to the manuscript was to write the section on peripheral nerve disease and stroke sections and to critically revise the manuscript.

Dr. Rao is a Chief Strategy Officer at Q Therapeutics. Dr. Rao's contribution was to write the sections on eye disease and Parkinson's disease.

Dr. Svendsen has no disclosures to report. Dr. Svendsen's contribution to this manuscript was to write the sections on amyotrophic lateral sclerosis and Huntington's disease and to critically revise the manuscript. Dr. Svendsen led the effort.

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Introduction

Unlike other organs, the central nervous system (CNS) has a limited intrinsic capacity to regenerate following most types of injury, often leading to permanent disability. Stem cell trials for a variety of neurologic diseases provide patients and physicians with regenerative stem cell treatments that can potentially restore neurologic function previously lost due to disease, maldevelopment or trauma. In this review, we provide the current state of clinical stem cell research for several neurologic diseases in which stem cell trials are promising.

Goals of stem cell trials

The goal of regenerative stem cell trials in neurological diseases is to restore function that was lost due to the disease. Stem cells could achieve this goal in multiple ways. The most obvious way stem cells could restore function is to replace lost cells. In this model, the stem cells would be injected into the area of damage, differentiate into the lost cell type based on environmental cues, and reconnect with local circuits. Although several stem cell trials have shown a clinical benefit, many of them did not demonstrate a mechanism of cell replacement. Rather, the stem cells provided some other benefits. Some stem cells provided a local “neuroprotective” effect by secreting growth factors and stimulating anti-oxidants. Other stem cells appeared to provide trophic support while some stem cells only impacted the immune system, which indirectly benefited the nervous system.

In the area of regenerative neurological trials, we are still in the stage of first identifying potential benefits of stem cells, and then figuring out how the stem cells helped.

Stem cell types

We refer to “stem cells” as undifferentiated cells that can be cultured and expanded for transplantation into the CNS (Tai and Svendsen, 2004). Human pluripotent stem cells isolated from the inner cell mass of blastocysts (embryonic stem cells, ESCs) or derived from adult somatic cells using reprogramming factors (induced pluripotent stem cells, iPSCs) have the potential to become any cell type, for instance neural lineages, by using specific culture conditions. Multipotent neural stem cells isolated from fetal brain tissue are further along the developmental axis, and hence more limited in their cell fate potential. These progenitor cells are committed to becoming neural tissue but can still proliferate in culture. Stem cells from all along this spectrum have been investigated in animal models and human trials of neurologic disease.

In addition to embryonic and fetal stem cells there have been many clinical trials in neurology using mesenchymal stem cells (MSCs). These are non-hematopoietic stromal cells that originate in the bone marrow and other adult tissues. MSCs can produce a limited number of tissue types *in vivo* including cartilage, bone and fat. However, when infused into the circulation they have a unique ability to avoid the host immune system, release growth factors and modulate inflammation and dampen the immune response. These global properties, perhaps related to regenerating an aging immune system, explain some of the early benefits of MSC transplantation seen in a range of conditions from myocardial infarction to multiple sclerosis (Lalu *et al.*, 2012). MSCs are also under extensive

investigation for spinal cord and peripheral nerve injury and trials are underway or being established for stroke, amyotrophic lateral sclerosis (ALS) and other conditions (Supplementary Table 1). There are a range of sources of mesenchymal or mesenchymal-like stem cells being developed for use in neurological conditions including umbilical cord blood and adult adipose tissue.

Two other cell types have been studied as potential candidates for neural regeneration that can be isolated from adult humans – Schwann cells and olfactory ensheathing glial cells (OEGs). These are non-CNS supportive cells and are responsible for axonal growth and targeting of peripheral and olfactory nerves, respectively. They are mature cells but similar to stem cells, they can proliferate, migrate and respond to their local environment. The advantage of these cells is a potential autologous supply of tissue with defined differentiation capacity to overcome safety and immunological barriers.

Most agree that other than in the hippocampus there is little stem cell regeneration in the adult human brain that involves long axonal connections. Current regenerative neurology efforts are therefore primarily based on promoting a supportive local environment for the function of remaining neuronal circuits.

Current State of Regenerative Stem Cell Therapies

Demyelinating diseases and spinal cord injury

Most demyelinating diseases are relapsing-remitting autoimmune conditions such as multiple sclerosis that cause inflammatory-mediated damage, especially to myelin. Spinal cord injury, though not considered a demyelinating disease, is included in this section because of the important contribution of demyelination to neurologic dysfunction after trauma (Waxman, 1989). The primary goal for regeneration in demyelinating conditions and trauma is to remyelinate otherwise healthy, intact axons. To that end, several companies and academic groups have developed stem cells designed for transplantation into the area of the demyelinated lesion, intended to differentiate in response to the local environment and produce functional myelin. While animal studies have suggested this may be possible, no human study has yet definitively demonstrated this objective (Walczak *et al.*, 2011).

Currently, there are over 20 ongoing stem cell trials for demyelinating diseases and traumatic spinal cord injury worldwide (Supplementary Table 1). The majority of these trials offer MSC infusions (intravenous and/or intrathecal) or surgical transplantation into the lesion. Four published studies of autologous MSC infusions for multiple sclerosis suggested some improvement in neurologic function, but the mechanism of action could not be conclusively based only on remyelination (Mohyeddin Bonab *et al.*, 2007, Karussis *et al.*, 2010, Yamout *et al.*, 2010, Connick *et al.*, 2012). One of these studies found that mesenchymal cell infusions led to an increase in regulatory T cells and a decrease in lymphocyte proliferation, suggesting a beneficial immunomodulatory effect (Karussis *et al.*, 2010). In addition, neuroprotection or trophic factor production by MSCs could provide a favorable local environment for healing and regrowth (Chiu and Rao, 2011). A fifth completed phase I study at the Cleveland Clinic reported they had reached their safety

endpoints (A Bar-Or, 2014). All of the studies demonstrated the relative ease and safety of this approach, contributing to the large number of MSC trials taking place worldwide.

Although it has been suggested that MSCs can migrate to the brain and differentiate into neurons, in most studies, the vast majority of these transplanted stem cells do not appear to survive nor remyelinate (Mezey *et al.*, 2003). Thus several groups have focused on transplantation of neural stem cells derived from embryonic, fetal and adult stem cells for the treatment of demyelinating conditions. The Geron Corporation performed the only neurologic trial employing embryonic stem cells. Oligodendrocyte precursors derived from this stem cell line, originally created by Dr. James Thomson at the University of Wisconsin-Madison in 1998 (Thomson *et al.*, 1998) and approved by the Food and Drug Administration (FDA) in 2010, were tested for safety and efficacy in five patients with acute spinal cord injury. The study ended prematurely in 2012 due to financial constraints (Scott and Magnus, 2014) but the five subjects continue to be followed for safety. None of the five suffered any adverse effect but, unfortunately, none of them have made any significant recovery from their traumas.

There are three companies using fetal or adult-derived neural stem cells for treatment of demyelinating conditions. Stem Cells Inc.'s (CA, USA) propriety cell line, HuCNS-SC, was the first neural stem cell line to be transplanted into humans. Six children with Batten's disease, a lysosomal storage disease of neurons, received a transplant between 2007 and 2009. Although the course of the disease was unchanged, the trial demonstrated the safety and tolerability of fetal neural stem cell transplantation (Stem Cells Inc. Company Bulletin, 2010). In a recently completed trial for Pelizaeus-Merzbacher disease, a pediatric dysmyelination disorder, administration of the HuCNS-SC line resulted in signs of myelination by magnetic resonance imaging and modest changes were detected in neurologic function (Gupta *et al.*, 2012). Based on animal models and human imaging, Stem Cells Inc. proposes the mechanism of action of the HuCNS-SC line to be new myelin production which, if confirmed in their recently launched phase II study, would be the first demonstration of regenerative stem cell therapy for a demyelinating disease. Stem Cells Inc. is also testing the efficacy of their HuCNS-SC line in subacute to early chronic spinal cord injury in a phase I/II trial in Switzerland and Canada. The 12-month interim data report of the first cohort of completely injured patients from this trial announced expected sensory gains, which correlate with positive changes in electrophysiology (Stem Cells Inc. press release February 2015). Neuralstem (Rockville, MD) is the second company to develop a fetal neural stem cell line (NSI-566) for the regenerative treatment of chronic spinal cord injury. This same line is currently approved by the FDA for investigation in amyotrophic lateral sclerosis (ALS, see section below for more details). The third company to consider demyelinating diseases, Q therapeutics, differentiates their stem cells one step further from a neural stem cell into a glial restricted precursor cell (GRP). GRPs are limited to become either oligodendrocytes or astrocytes, but no longer neurons. The advantage of using a more differentiated glial precursor cell in demyelinating diseases is that avoiding the unnecessary generation of neurons provides a greater focus on producing myelin and supportive glial cells. Q therapeutics has not yet announced a start date for their trial in demyelinating disease. Even further differentiated toward oligodendrocytes than GRPs is the oligodendroglial precursor cell (OPC), a stem cell that can only differentiate into

oligodendrocytes. OPCs harvested from human brain tissue are being developed for trials in multiple sclerosis and tested in pediatric dysmyelinating diseases including Pelizaeus-Merzbacher, Krabbe's and Tay-Sachs by Dr. Stephen Goldman at the University of Rochester (Supplementary Table 1).

Schwann cells and olfactory ensheathing glial cells, while not technically stem cells, are also being investigated for their ability to remyelinate or regenerate in demyelinating conditions. In fact, the first regenerative cellular trial in a demyelinating disease was done at Yale University (the Myelin Project) using Schwann cells from the ankle stereotactically injected into the posterior subcortical area of patients with multiple sclerosis (unpublished). The hypothesis was that Schwann cells could replace the dead oligodendrocytes; however, the study was discontinued after investigators could find no evidence of Schwann cell survival in the first three subjects. Recently, the Miami Project at the University of Miami launched a phase I safety trial using a similar approach of transplanting Schwann cells into patients with spinal cord injury. At the time of this publication, two patients have been enrolled without incident. Similar to Schwann cells, olfactory ensheathing glial cells (OEGs) are myelin-producing supportive cells for olfactory axons exiting the CNS. There is one trial currently recruiting in Poland to use OEGs in spinal cord injury. There has been considerable press interest in the first case recruited for this study in which the participant appeared to improve from complete paralysis of the legs to some voluntary movements (Tabakow *et al.*, 2014).

Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease)

In sporadic amyotrophic lateral sclerosis (ALS), both upper motor neurons (in the cortex) and lower motor neurons (in the spinal cord) degenerate for unknown reasons leading to paralysis and death. There are no effective treatments. In familial ALS there are a few known mutations but these account for only approximately 10% of all cases (Iguchi *et al.*, 2013).

Original goals of stem cell transplantation in ALS were to replace the lost motor neurons in the spinal cord. However, it was soon realized that this is an extremely difficult task given the distance that a new motor neuron would have to project its axon, the resistance of CNS white matter to support axonal growth, and early evidence suggesting that the toxic environment within the degenerating spinal cord might not support the newly transplanted motor neurons (Haidet-Phillips *et al.*, 2011). Elegant studies spawned a new era of glial cell transplantation based on surrounding dying motor neurons with supportive astrocytes, which may also be affected in ALS (Mazzini *et al.*, 2012). Previous studies showed that both rodent and human astrocytes could survive and integrate into the spinal cord of familial ALS mice and rats, and did not appear to be negatively affected by the environment (Lepore *et al.*, 2011). Effects ranged from just survival with no adverse effects on disease progression to motor neuron protection and in some cases a reduction in paralysis. Several animal studies also report beneficial effects of mesenchymal cells either given peripherally or injected directly into the cisterna magna or even spinal cord parenchyma (reviewed by Gowing and Svendsen, 2011).

Based on this encouraging laboratory data, a number of clinical trials in humans were launched. The first, led by Dr. Mazzini in Italy, used MSCs injected into the spinal cord of

19 ALS patients. There were no negative outcomes reported suggesting MSCs could be injected safely, but they reported no neurologic improvement in patient outcome either (Mazzini *et al.*, 2012). An important factor in this study could be that mesenchymal cells only survived a short time in the spinal cord. Another more recent trial by the company Brainstorm Cell Therapeutics (Israel) transplanted similar MSCs treated with a propriety method to induce them to secrete glial cell line-derived neurotrophic factor (GDNF) into the cisterna magna of 12 patients. Again no adverse effects were reported, but there were no reports of overall improvement either, although the trial is still under way (Brainstorm Press Release, January 5, 2015).

A third stem cell trial in ALS run by Nicholas Boulis and Jonathon Glass at Emory University sponsored by Neuralstem (Rockville, MD) pioneered the first American trial using neural stem cells derived from human fetal spinal cord tissue. Pre-clinical work demonstrated that transplantation of these cells into rodent models of ALS resulted in both neuronal and glial cells, which enhanced survival of motor neurons, although effects on paralysis were transient (Hefferan *et al.*, 2012). Based on these promising animal studies, a phase 1 trial enrolled 15 patients into a novel “risk escalation” trial design that began with 5 unilateral 10 microliter injections in the lumbar spinal cord in non-ambulatory ALS patients, and was then expanded to bilateral lumbar injections in non-ambulatory patients, then to bilateral lumbar injections in ambulatory patients and finally to unilateral C3–C5 cervical spinal cord transplants in ambulatory patients. The final three procedures were performed on prior lumbar transplant recipients. The trial found no lasting neurological sequelae of transplantation (Glass *et al.*, 2012, Riley *et al.*, 2012). Analysis of postmortem tissue in 6 patients demonstrated survival of transplanted cells in the spinal cord. While this trial has yielded anecdotal evidence of improvements in motor function, conclusive improvement has not been demonstrated. Again we emphasize extreme caution when reporting these early phase I trial results. The FDA has approved a second NeuralStem trial funded by the National Institutes of Health that will escalate cell dosing in the cervical spinal cord, first to involve bilateral injections, then increasing cell concentration and number of injections. The third group will receive 20 cervical injections and 20 lumbar injections bilaterally. Finally, Q-therapeutics is planning to use their glial-restricted precursor cells (described above in the demyelinating disease section) for astrocyte replacement therapy in ALS. The combination of all of these studies will likely provide valuable insight into the pathogenesis of ALS as well as progress in our effort to restore motor function.

Stroke

Recovery after stroke is due to either plasticity of other brain regions outside the area of damage or recovery of damaged areas after re-perfusion. Four clinical trials using stem cells in stroke have been completed to date using human neural stem cell lines (Kondziolka *et al.*, 2000, Kondziolka *et al.*, 2005), xenografted fetal pig cells (Savitz *et al.*, 2005), and MSCs (Bang *et al.*, 2005). The human cell lines appeared safe but efficacy studies are lacking. There is currently one ongoing regenerative stem cell trial in stroke sponsored by ReNeuron (Glasgow University, Scotland). Five patients with ischemic stroke have been transplanted with human neural stem cells and four more subjects will be recruited. A recently released interim report suggests that all five patients have made mild to moderate improvements, but

these data have not been subject to peer review. As described for other neurodegenerative conditions, replacing neurons in stroke will be a challenge. However, increasing plasticity using stem cells may be an important way to enhance recovery following stroke damage (Andres *et al.*, 2011). A number of recent pre-clinical studies in stroke models using embryonic stem cell-derived neural progenitors or fetal progenitors portend a growing interest in this approach (reviewed by (Lindvall and Kokaia, 2011), but the timeline to the clinic for these approaches is not clear.

The wide use of MSCs and some evidence that they can reduce the symptoms of stroke in animal models through a combination of immunomodulatory or anti-inflammatory effects and growth factor release have led to several stroke trials with MSCs (Bliss *et al.*, 2007, Shen *et al.*, 2007). In a trial of 52 stroke patients in South Korea, 16 received an intravenous injection of MSCs and 36 did not. Over 5 years, patients receiving MSCs had a greater likelihood of survival and lower disability compared to patients receiving no cells (Lee *et al.*, 2010). A phase I study in India using intravenously infused MSCs in 11 ischemic stroke patients proved safe and effective in the majority of their subjects followed over 1 year (Prasad *et al.*, 2012). This same group recently completed their phase II study in ischemic stroke and confirmed that intravenous MSCs are safe in 58 patients with ischemic stroke, but was unable to demonstrate any clinical benefit (Prasad *et al.*, 2014). Over 20 ongoing trials using MSCs in ischemic stroke are currently underway worldwide. Olfactory ensheathing glial cells are also being tested in stroke in one ongoing human trial (Supplementary Table 1).

Huntington's disease

Huntington's disease (HD) is a tri-nucleotide (CAG)-repeat disorder where over 30 repeats in the *huntingtin* gene leads to severe psychiatric problems followed by choreic movements and ultimately death. Pathology includes massive shrinkage of the striatum followed by equally severe loss of the cortex (Vonsattel *et al.*, 2011). Pioneering work by Lindvall, Dunnet, Isacson and others showed that primary human fetal striatum could survive and partially reestablish a new striatum in several animal models of HD – often receiving cortical afferent input and sending efferent connections into the globus pallidus (Isacson *et al.*, 1986, Lindvall and Bjorklund, 2000). Another group has shown that brain-derived neurotrophic factor (BDNF) can activate resident progenitor cells in the subventricular zone to migrate to the striatum and replace lost neurons (Benraiss *et al.*, 2013). Based on these encouraging animal studies, there have been a number of completed and ongoing clinical trials using primary human striatal tissue (Bachoud-Levi *et al.*, 2006, Gallina *et al.*, 2010, Barker *et al.*, 2013). However, the efficacy of these studies has been disappointing with no real improvements in neurologic function or mortality, even if there was apparent stem cell graft survival.

There have been a number of studies showing that human embryonic or fetal neural stem cells can survive transplantation into the striatum of HD mouse or rat models and in some cases provide significant functional benefit (McBride *et al.*, 2004, Aubry *et al.*, 2008). When modified to produce GDNF or insulin growth factor, they can have further beneficial effects (Ebert *et al.*, 2010). Despite these encouraging results, there are no embryonic or fetal-

derived neural stem cell transplant trials currently underway for HD. Mesenchymal stem cells have also been shown to have some trophic benefit when directly injected into the brains of animals with HD, an effect significantly enhanced when they are modified to release BDNF (Moraes *et al.*, 2012). A California Institute of Regenerative Medicine grant is currently allocated for pre-clinical studies to move MSC transplantation forward into patients. However, as mentioned previously, MSCs may survive only short-term after transplantation into the brain parenchyma or elsewhere in the body. Thus, this approach remains somewhat controversial.

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder resulting of a loss of midbrain dopaminergic neurons. Although there is no cure for PD, there are a variety of pharmacologic treatments to mitigate some of the functional deficits due to dopamine depletion. In addition, deep brain stimulation for PD is an accepted treatment option designed for patients who respond to dopamine supplement but who cannot tolerate the medication side effects. This same population is also the ideal group for stem cell transplantation trials as these patients are already undergoing invasive surgery into the basal ganglia.

A challenge for stem cell transplantation is that ectopic placement of cells would not likely be integrated into the normal brain circuitry. Even if placed in their site of origin, i.e., the substantia nigra, new dopaminergic neurons do not regenerate axons to the striatum. There have been hundreds of PD patients worldwide who have undergone striatal injections of human fetal mesencephalic stem cells containing post-mitotic dopaminergic neurons with varying results and complications (Lindvall and Bjorklund, 2004). Five open label clinical trials conducted between 1999 and 2003 all showed a clinical benefit characterized by symptomatic relief lasting up to 24 months and a reduction in L-dopa requirement (Hagell *et al.*, 1999, Hauser *et al.*, 1999, Brundin *et al.*, 2000, Freed *et al.*, 2001, Olanow *et al.*, 2003). In some patients, there was an associated increase in fluoro-dopa Positron Emission Tomography signal in the transplant site and histopathological analysis showed survival of up to 138,000 dopaminergic neurons with neurite outgrowth and synaptic connections (Kordower *et al.*, 1998). These studies suggest that transplantation of fetal-derived post-mitotic dopaminergic cells, though not technically stem cells, can replace lost cells in PD. However, graft-induced dyskinesias occurring in more than half of the PD patients were the major side effect in all of fetal stem cell transplantation studies (Politis and Lindvall, 2012). The mechanism underlying these dyskinesias is not well understood, but it may be related to serotonergic neurons in the transplant or imbalances of dopamine production.

One hindrance of cell replacement therapy for PD has been the lack of an abundant, reliable and reproducible source of dopaminergic neurons. Recent advances in iPSC biology to successfully differentiate pluripotent cells into authentic A9 dopaminergic neurons and in Good Laboratory Practice manufacturing of these cells open a new avenue for cell replacement therapy (Sanchez-Danes *et al.*, 2012). Several groups have initiated pre-clinical studies evaluating the use of either fetal, ESC or iPSC-derived dopaminergic cells (Ambasudhan *et al.*, 2014).

Another limiting factor in the success of using stem cells in Parkinson's disease is the host environmental impact on the stem cell transplant. Several studies have demonstrated that young neuronal stem cells exposed to Parkinson's diseased brains developed Lewy bodies as evidenced by alpha-synuclein, ubiquitin, and thioflavin-S staining. Additionally, there was loss of dopamine transporter-immunoreactivity in grafted neurons (Kordower *et al*, 2008).

Rather than replacing lost dopaminergic neurons, investigators have argued that trophic support, immunomodulation, and neuroprotection provided by transplanted MSCs may be a better approach to treat PD. With this in mind, MSCs are being used for PD in two small trials launched to determine the feasibility and usefulness of this approach (Supplementary Table 1). In addition, investigators have proposed *ex-vivo* gene therapy, specifically with the use of transplanted astrocytes and the use of retinal pigment epithelial cells to delay the progression of PD. One important trophic factor that may improve survival of dopaminergic neurons in PD is GDNF. Engineering human neural progenitor cells to secrete this powerful growth factor represents a novel combination of stem cell and *ex vivo* gene therapy approaches as a mechanism to enhance host dopamine survival and maintain synaptic integrity (Behrstock *et al.*, 2006).

Diseases of the Eye

Diseases of the eye amenable to cell replacement strategies include Retinitis Pigmentosa (RP) and Macular Degeneration (MD). RP is a genetic condition leading to a gradual loss of sight over time due to damage to the retinal cells or the retinal pigment epithelial layer (RPE). MD is a condition of retinal damage and detachment most often caused by accumulation of cellular debris in the RPE layer between the choroid and the retina (termed dry or age-related macular degeneration (AMD)). Several animal studies support the theory that replacing the damaged RPE cells or providing cells that provide general trophic support may prevent further degeneration of the retina and preserve vision (reviewed in Binder *et al.*, 2007). With recent advances in the differentiation of cells, it has become relatively straightforward to obtain differentiated, functional RPE cells. More importantly it is now technically possible to obtain sheets of cells on either a native or synthetic scaffold, and instruments have been designed to enable insertion of a sheet of RPE in the subretinal space (Carr *et al.*, 2013). Janssen Biotech (Philadelphia, PA, USA) has developed a microcatheter being tested to deliver human umbilical tissue-derived stem cells into the subretinal space of patients with dry AMD.

Presently, there are two ongoing phase I/II open-label studies of intravitreal/subretinal-injected RPE cells in dry AMD (Supplementary Table 1). Advanced Cell Technology (CA, USA) is performing a safety and tolerability study in AMD patients receiving intravitreal injections of human ESCs differentiated to RPE cells. They recently reported on one patient whose vision improved from 20/400 to 20/40 following treatment, but details on the other subjects have not yet been released. In Korea, a phase I/IIa trial also using ESC-derived RPE cells for dry AMD launched last year. A phase I trial by Pfizer in London is planning to use human ESC-derived RPEs for treatment of wet AMD, a rarer but more severe form associated with choroid blood vessel proliferation.

As in other neurologic diseases, investigators have also evaluated MSC transplantation for treatment of AMD as well as human umbilical tissue-derived cells (Janssen Biotech, Philadelphia, PA, USA) and neural stem cells (StemCells Inc., Newark, CA, USA). In addition, stem cells and growth factor release have been used in a combined treatment by Neurotech (Cumberland, RI, USA) in collaboration with the National Eye Institute (Bethesda, MD, USA), which demonstrated the safety and potential efficacy of transplanted RPE cells designed to secrete ciliary neurotrophic factor, a neuroprotective cytokine. The treatment appeared to slow the progression of visual loss but further studies are necessary to confirm these findings (Kauper *et al.*, 2012). In September 2014, the first clinical procedure of transplanted iPSCs was performed in Kobe, Japan for a woman with AMD. The iPSCs were generated from the patient's skin cells and differentiated in the lab before being injected back into the same patient's eye. The approach using autologous iPSCs reduces the risk of graft rejection, need for prolonged immunosuppression and ethical issues related to use of embryonic stem cells; however, the safety of iPSCs has yet to be demonstrated in humans.

Peripheral Nerve Disease

While the peripheral nervous system maintains an inherent capacity for regeneration that is largely absent from the CNS, recovery from focal and diffuse neuropathy, nerve injury, and neuralgia remains poor. Unlike the CNS, the lower motor neurons and dorsal root ganglion neurons shift from a transmission phenotype into a growth phenotype after injury creating axons capable of regrowth. At the site of injury and in the distal stump, Schwann cells proliferate, secrete growth factors creating a permissive extracellular matrix, and express cell surface adhesion and guidance molecules (Dyck, 1992). However, the capacity of motor and dorsal root ganglia neurons to support axonal regeneration diminishes with time, as does the ability of the distal stump to support regenerating axons, frustrating efforts at nerve repair (Hoke, 2006).

The goal of peripheral nerve transplantation of stem cells is to enhance the capacity for regeneration by stimulating the proximal stump cells with growth factors, and repairing the distal stump by replacing diminished native Schwann cells either with new Schwann cells or alternate cells with similar capacities. Ongoing research efforts to enhance the capacity of grafts to bridge gaps in injured nerves by seeding either acellular grafts or artificial conduits may be able to assist insufficient endogenous repair processes (Walsh and Midha, 2009).

Stem cell applications in peripheral nerve disease have not reached human trials; however, a variety of cell types have been used in *in vitro* and *in vivo* models. The most commonly applied stem cell type is adult MSCs. MSCs have been directly injected and used to seed grafts in rats with one report in primates (Hu *et al.*, 2007). The majority of these animal studies reveal improvement in histological and electrophysiological measures of recovery, with several showing improved function (Keilhoff *et al.*, 2006, Wakao *et al.*, 2010).

In addition to adult MSCs, animal experiments using embryonic and fetal stem cells have shown benefit in peripheral nerve diseases. Cui *et al.* (2008) demonstrated in rodents that ESCs differentiated into a neural lineage could support enhanced regeneration when delivered to a sciatic gap. Histological analysis suggested that Schwann cell differentiation

after transplantation with accompanying remyelination might have contributed to functional regeneration. Other studies have demonstrated an ability to produce myelin with neural progenitors taken from the fetal hippocampus and neural crest (Aquino *et al.*, 2006).

Unfortunately, a major shortcoming in the field is that the short gap repairs of nerve regeneration in small animal models do not recapitulate the chronic denervation conditions seen in human nerve regeneration. A more appropriate rodent model is to use a chronic denervation and delayed nerve repair model in which the chronic denervation changes in the distal stump mimic the conditions of human nerve regeneration. As in other neurologic diseases, *ex vivo* manipulation of stem cells has been used to augment their capacity to support axonal regeneration. Using the chronic denervation and delayed nerve repair model, Heine *et al* (2004) transplanted neural stem cells engineered to secrete GDNF into the distal stump, which enhanced regeneration.

Conclusions

It is difficult to compare the efficacy of different stem cells or compare them to small molecule-based therapy. However, this comprehensive review highlights that, while no single cellular source appears as a first choice for regenerative therapy, there are several potential sources that offer substantial promise.

For demyelinating diseases such as MS, the diffuse nature of the disease involving the entire CNS presents a challenge for delivery of regenerative stem cells. Perhaps a focal proof-of-concept model such as transverse myelitis or optic neuritis can demonstrate the regenerative capacity of neural stem cells. However, work with human fetal oligodendrocytes appears very promising. In consideration of MSCs for their immunologic and supportive roles, we are excited about the potential use in MS given their safety record.

Replacing the lost motor neurons in ALS with exogenous stem cell transplantation has proven to be difficult as new ones may also be damaged by the diseased environment. In addition, the new spinal motor neurons have the difficult task of integrating with the brain motor neurons and projecting their axons all the way to the muscle. There is an emerging consensus that rather than replacing lost motor neurons, transplanted stem cells provide a supportive, trophic environment that preserve remaining motor neurons.

Neuronal replacement using stem cell transplantation following stroke is not well supported in the literature at this time. Ongoing challenges for stem cell regenerative trials in stroke include method of delivery, optimal timing and location, heterogeneity of disease and risk of triggering inflammation. Using stem cells to modify the environment after stroke to enhance plasticity and thus recovery are promising. MSCs have potential to improve outcome after stroke by providing a supportive, healing environment and modifying the patient's inflammatory response.

Primary human striatal transplant trials in Huntington's Disease have been safe but disappointing in terms of efficacy. Fetal neural stem cell transplant trials have been encouraging in animal models and have yet to be translated to humans. MSC transplantation may provide a mechanism to deliver trophic factors but will not lead to neural regeneration.

Of all neurologic diseases, the promise of cell replacement strategies in PD has been the most extensively investigated thus far. The technology for producing dopaminergic neurons from pluripotent cells is advanced and ready for clinical development. While challenges with dopamine neuronal replacement remain including lack of treatment of the systemic symptoms of PD, repairing the dopaminergic component of PD appears to be beneficial for patients.

Stem cell treatment for acute macular degeneration is likely to become the first stem cell-based treatment for a neurologic disease. There are several well-conducted pre-clinical and early clinical studies that support the use of RPEs to support and/or replace the damaged epithelium in MD.

Stem cell therapies for peripheral nerve disease have shown benefit in animal models but have yet to translate to human trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Dr. Soshana Svendsen at Cedars-Sinai for critical review of the manuscript.

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Highlights

- Stem cell therapies are currently being tested in a number of neurological diseases.
- No stem cell therapy has yet been approved, but the science is progressing.
- This review summarizes the current state of the field of regenerative neurology.