

Stem Cells to Treat Neurological Diseases - Implications for Neurosurgery

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In recent years, there has been great interest in the use of stem cells for the treatment of neurological diseases. Different sources of cells for transplantation have been used, including neural progenitor cells, neural stem cells, or embryonic stem cells. This research has spurred many debates in the scientific community as well as in the lay press as to the feasibility, safety, and ethics of such work. Studies are currently underway to define the potentials of stem cells in the treatment of human neurological diseases. As neural cellular replacement therapy develops, diseases that have classically not been treated surgically will be introduced within the realm of neurosurgery. It is thus imperative that neurosurgeons have an understanding of and participate in research related to this field. Stem cells are defined as immature, uncommitted cells that are able to self-replicate in tissue culture, and differentiate into most lineages of cells. Embryonic stem cells (ES cells) are derived from the inner cell mass of an embryo in the blastocyst stage and are totipotent, with the ability to form all cell types and tissues from all embryonic germ layers, including neural tissues. (1,2) Multipotent neural stem cells (NSC's), which have the ability to differentiate into all neural, and glial cell types, are derived from the subventricular zone or germinal matrix of a developing fetus brain and propagated in specific growth factor enhanced media. (3,4) These cells have the ability to form neurons, astrocytes, and oligodendrocytes given the appropriate developmental cues or culture conditions. Indeed when transplanted into the developing nervous system, NSC's disseminate throughout the CNS and integrate within the developing neural networks. Both ES cells and NSC's have been investigated for their potential role in the treatment of neurological disease. Previous research has looked at the transplantation of fetal brain tissue grafts for neurological disorders, most notably for Parkinson's disease. (5-11) These studies have shown that cellular replacement therapy may be a promising methodology to treat neurodegenerative diseases. A drawback of this therapeutic approach is the ethical concerns of obtaining sufficient tissue grafts from embryonic brains to treat a large number of patients. Stem cells, on the other hand, are able to provide an unlimited source of donor cells for transplantation through in vitro expansion in an undifferentiated state. The use of stem cells has been proposed for disorders ranging from stroke, to neurodegenerative diseases including Parkinson's disease and Huntington's disease, to spinal cord injury, to demyelinating disorders. In experimental models, neural stem cells have been shown to have the ability to engraft and integrate into diseased CNS, repopulate specific types of degenerating cells, and express therapeutic foreign genes.(4) Postulated mechanisms of action that can be harnessed for therapeutic value include 1) replacement of degenerating, or injured neural cells, 2) secretion of neurotrophic factors to support host neurons and glia, and 3) delivery of a deficient factor, such as a gene product, or neurotransmitter. This article will review five recent reports of ES and NSC transplants in the treatment of animal models of specific neurological diseases. While these studies provide optimism

that stem cell technology will be beneficial as a therapeutic strategy to treat neurological disease, they are only preliminary in nature. Further investigation is necessary to precisely define the cell biology, safety, and potential therapeutic benefits of transplanted stem cells prior to introduction into human trials.

PARKINSON'S DISEASE [1] EMBRYONIC STEM CELLS DEVELOP INTO FUNCTIONAL DOPAMINERGIC NEURONS AFTER TRANSPLANTATION IN A PARKINSON RAT MODEL 12 PROC NATL ACAD SCI USA 99, 2344-9 (2002).

Information

The investigators transplanted mouse embryonic stem (ES) cells in low concentrations into the striatum of 6-OHDA lesioned rats, and assessed for cell engraftment, differentiation into a dopaminergic phenotype, and functional recovery *in vivo*. Sprague-Dawley rats received stereotactic unilateral intrastriatal injections of 6-OHDA into the median forebrain bundle. Rats were tested for successful lesioning with amphetamine-induced turning studies. Rats with >500 ipsilateral turns were selected for cell transplantation. The investigators transplanted 1000-2000 undifferentiated ES cells into the striatum on the lesioned side in 25 rats, while 13 rats received sham surgery (injection of medium). Rats underwent behavioral analysis (amphetamine-induced rotation studies) at 5, 7, and 9 weeks post-transplant, positron emission tomography and functional MRI at 9 weeks, and immunohistochemical analysis at 14-16 weeks. Within the group of 25 transplanted rats, 6 showed no graft survival, 5 died before study completion and were found to have teratoma-like tumors at the transplantation site, 9 underwent behavioral analysis, and 5 were sacrificed for histology. Immunohistochemistry showed the presence of dopaminergic neurons within the graft. Antibodies against the markers tyrosine hydroxylase (TH), neuronal nucleus (NeuN), aromatic amino acid decarboxylase (AADC), dopamine transporter (DAT), calretinin, calbindin, and aldehyde dehydrogenase 2 were used to show dopaminergic phenotype. The graft also contained serotonergic-phenotype (5-HT) neurons which expressed 5-HT, AADC, and NeuN. These dopaminergic and serotonergic neurons were shown to be derived from transplanted cells using a mouse specific antibody, anti-M6. Behavioral recovery was assessed measuring amphetamine-induced rotational behavior. Rats that received ES cell grafts showed a gradual decrease in rotational behavior which was significant by 7 weeks and persisted to 9 weeks. Sham-injected animal showed no change from their baseline turning rate. Functional imaging was performed to assess dopaminergic differentiation of donor cells, graft survival, and functional integration into the host CNS. Carbon-11-labeled 2 β -carbomethoxy-3 β -(4-fluorophenyl) tropane ($[^{11}\text{C}]$ CFT) uptake increase on PET scanning at the graft site to 75-90% of the intact side demonstrated that the transplanted cells differentiated into dopaminergic neurons. Sham animals showed activity at <25% of the intact side. Functional MRI was used to assess cerebral oxygen consumption rate (rCBV) in response to amphetamine challenge. Grafted animals showed increased rCBV in the cortex and striatal regions, indicating that the ES cells grafts had functionally integrated within the host brain.

Analysis

Previous studies using fetal mesencephalic tissue for transplantation into both animal models and in patients has shown that cellular replacement may be a promising therapeutic approach to the treatment of Parkinson's disease. However, there are concerns about the ethics and the feasibility of obtaining fetal tissue in sufficient quantities to treat a large number of patients with Parkinson's disease. Since ES cells have been shown to be able to differentiate into dopaminergic neurons, and have the capability of propagating in tissue culture, they provide an alternative cell source for transplantation. Previous studies have shown dopaminergic differentiation in vitro. This study by Bjorklund et. al shows that ES cells can differentiate into a dopaminergic-phenotype in vivo after transplantation into a lesioned striatum, and functionally integrate within the host CNS. While this is a promising finding, the article also demonstrates some of the obstacles that lie ahead in ES cell transplantation research. The authors reported that 6/25 transplanted animals had no surviving cells at the time of analysis. The graft survival rate will need improvement prior to proceeding to clinical therapy. The low graft survival rate may be due to multiple factors which need to be studied; transplantation surgical techniques may need to be improved; the timing of transplantation may play a role due to the presence or absence of local signals related to neuronal death that induce not only graft survival, but also differentiation into dopaminergic neurons; ES cells may need trophic support in the form of exogenously added factors prior to, or during transplantation; and the level of immunosuppression may need to be improved. ES cell transplantation is of interest due to the multi-potent nature of the cells, however this characteristic may also be detrimental. In this study, 5/25 animals died prior to study completion and on analysis had teratoma-like tumors at the transplantation site. The multi-potent nature of the cells allows them to differentiate into all germ-cell layers, introducing the risk of teratoma growth where the cells are transplanted. The authors show that transplantation of ES cells in lower concentrations decreases this risk, presumably due to decreased cell-to-cell signalling, however the rate of teratoma formation still persists. Studies looking at possible pre-differentiation of cells, or the addition of factors that direct a neural lineage may be necessary to make this therapy safer. There are interesting neurobiological findings with this and similar studies which show that the default pathway of differentiation of ES cells is to neurons, and more specifically to dopaminergic neurons. Previous studies by these authors show that ES cells transplanted outside of the central nervous system will differentiate into dopaminergic neurons. This characteristic of ES cells makes them especially suitable for the treatment of Parkinson's disease and provides optimism that cell transplantation may be a feasible and effective therapy.

Huntington's Disease

Neural transplantation studies using fetal brain allografts have also been performed in animal models of Huntington's disease, both in lesioned rats (13-15) as well as in primates (16,17). These studies have shown that cell transplantation can repopulate the lesioned striatum, survive, and integrate within the central nervous system. Transplanted animals also were seen to have functional and behavioral improvements. Cellular replacement strategies have been also been attempted in patients with Huntington's disease, (18-20) showing improvement or stable motor and cognitive function in small numbers of patients

with surviving grafts. These preliminary studies in animal models and in patients provide evidence that cellular replacement may be a potential treatment for Huntington's disease. However, this approach suffers from the same limitations as the trials using fetal allograft brain tissue in Parkinson's disease; ethical considerations and difficulties in obtaining sufficient graft material for large numbers of patients. Since the principle of cellular replacement into the striatum has shown to be promising, NSC's and ES cells, which self-replicate in tissue culture, may provide an unlimited source of cells for grafting in this disease process, as with Parkinson's disease.

DEMYELINATING DISEASE [2] EMBRYONIC STEM CELL-DERIVED GLIAL PRECURSORS: A SOURCE OF MYELINATING TRANSPLANTS 21 SCIENCE 285, 754-6 (1999).

Information

This study looks at the potential for ES cells to be used as a source of myelinating cells in diseases with disorders of myelin. The authors capitalized on previous knowledge of factors used to differentiate neural stem cells to induce differentiation of ES cells into precursors of specific glial cells in vitro prior to transplantation. Murine ES cells were propagated in tissue culture media that contained growth factors thought to induce glial precursors; basic fibroblast growth factor (FGF2), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF). In vitro, cells grown in different combinations of these growth factors expressed membrane proteins indicating they were glial precursors (immunoreactivity to mAb A2B5). Withdrawal of growth factors resulted in cellular differentiation into astrocytes and oligodendrocytes which were immunoreactive to glial fibrillary acidic protein (GFAP) and O4, respectively. These ES cell-derived glial cells were transplanted into a rat model of myelin disease to study their potential to myelinate axons in vivo. The myelin deficient (md) rat is a model of the X-linked human disease Pelizaeus-Merzbacher Disease (PMD), in which a deficiency of myelin proteolipid protein (PLP) results in dysmyelination. Seven day-old md rats received a single injection of 100,000 glial precursor cells into the dorsal column at the thoracolumbar region of the spinal cord. Histological analysis showed that rats without transplants have a deficiency of myelin. However, in 6/9 transplanted rats, myelin sheaths were seen surrounding host axons 2 weeks after transplantation. Injected cells producing PLP positive myelin sheaths had migrated up to 2mm away from the primary injection site. These myelinating cells were shown to be donor-derived using mouse specific markers, demonstrating that transplanted glial precursor cells differentiated from mouse ES cells have the potential to myelinate axons in the host CNS. Glial precursor cells were also injected into the ventricle of prenatal md rats to determine if myelination is possible in widespread regions of the CNS. Three-week old rats that had received intraventricular injections of glial precursor cells at embryonic day 17, showed PLP-positive myelin sheaths in the cortex, corpus callosum, hippocampus, thalamus and other regions of the brain. Myelinating cells were shown to be derived from transplanted cells using mouse-specific markers.

Analysis

Demyelinating disease can lead to severe neurological dysfunction and can be debilitating. This study provides evidence that ES cells may be used as an unlimited source of myelinating oligodendrocytes for transplantation in these types of disorders. Diseases in which there is widespread demyelination or lack of myelination pose a challenge to possible cellular therapies, due to the difficulty of delivery of cells throughout the CNS. The authors used intraventricular injection of cells in prenatal rats to overcome this obstacle and showed cell migration and myelination throughout different regions of the brain. Other studies have looked at intraventricular transplantation of NSCs in newborn shiverer mice, which lack myelin basic protein resulting in dysmyelination, demonstrating oligodendrocyte differentiation and myelination throughout the CNS.(22) Thus transplantation within the developing nervous system, utilizing normal migratory pathways, may allow widespread delivery of therapeutic cells. The authors noted that there was no teratoma or tumor formation in animals transplanted with the glial precursor cells. They postulate that pre-differentiation *in vitro* into glial precursors may eliminate totipotent ES cells that have the ability to form tissues of all germ lines. The follow-up period was short, however; this may provide a strategy to increase the safety of ES cell transplantation. Indeed, others have reported a lack of teratoma formation in animals transplanted with ES cells, which were pre-differentiated into glial precursors by different methods.(23).

SPINAL CORD INJURY [3] TRANSPLANTED EMBRYONIC STEM CELLS SURVIVE, DIFFERENTIATE AND PROMOTE RECOVERY IN INJURED RAT SPINAL CORD 24 NAT MED 5, 1410-2, (1999).

Information

This study investigated the potential of ES cells to engraft, survive, differentiate, and promote functional improvement in an rat model of spinal cord injury. The authors induced spinal cord injury at T9-10 in adult Long Evans female rats using a weight drop device; a 10 gram weight was dropped 25mm onto the exposed spinal cord. Rat locomotion function was followed using the Basso-Beattie-Bresnahan (BBB) open field rating scale. Baseline BBB scores were obtained on day 8 post-injury and ES cell transplantation was performed on day 9. Eleven rats received ~1x10⁶ ES cells, (pre-differentiated towards a neural lineage using retinoic acid for 4 days *in vitro*) injected into the syrinx cavity at the T9 level. Control rats (n=11) received injection of medium alone into the cavity. A third set of animals (n=11) received ROSA26 ES cells, which express β-galactosidase. ES cells were pre-labelled with bromodeoxyuridine (BrdU) to facilitate tracking *in situ*. Animals were sacrificed at 2-5 weeks post-transplantation for histological analysis. The results showed donor-derived ES cells within the spinal cord, both at the level of injection within the syrinx, as well as up to 8mm rostral and caudal to the transplantation site. Mouse-specific antibodies (M2) were used to detect donor cell processes within the transplanted spinal cords, which were absent in the sham-surgical animals. Transplanted ES cells expressed markers demonstrating differentiation, most commonly into oligodendrocytes (43% APC CC-1 positive), followed by astrocytes (19% GFAP positive), and neurons (8%

NeuN positive). Cells with oligodendrocyte markers were also positive for myelin basic protein (MBP). There was no teratoma formation noted. Functional performance was assessed with the BBB locomotion score. Animals were tested pre-transplantation and every week post-transplantation by examiners who were blinded to the treatment. Statistically different scores between ES cell and sham injected animals were recorded 2 weeks after transplantation. At one month, cell transplanted animals had a mean BBB score of 10.0 ± 0.4 and medium injected animals had a score of 7.9 ± 0.6 , the difference representing partial hindlimb weight-bearing and coordination in the ES cell treated animals. Transplantation of mouse neurons into the syrinx produced no BBB score improvement over vehicle-injected animals demonstrating that the functional recovery in ES cell animals was not due to an immune-mediated phenomenon based on the mouse xenograft into rat spinal cord.

Analysis

This study provides evidence that ES cell transplantation may provide some functional recovery in spinal cord injury. The BBB score improvement was modest in the cell-transplanted animals, however was statistically significant. Currently there are no clinical treatments for spinal cord injury that significantly improve function. An increase in strength to a partial weight-bearing level would be extremely beneficial in patients with spinal cord injury. Further understanding of the process leading to functional improvement after cell transplantation may allow for more optimal cell delivery techniques for this process. The authors postulate that the rapid improvement in BBB score (2 weeks) may be attributable to re-myelination of injured host axons. They argue that the high percentage of oligodendrocyte differentiation from donor-derived ES cells supports this hypothesis. Another possibility they propose is that transplanted ES cells provide growth factors that may support host-mediated regrowth. The authors did not address whether there was formation of a glial scar at the injury site, and whether the ES cells accentuated or diminished this response seen with spinal cord injury. Glial scar formation may explain the modest improvements in BBB score in the transplanted group. Others have investigated the possibility of minimizing glial scar formation and prevention of axonal regrowth using a spinal cord hemitranssection model in a rat, transplanting neural stem cells seeded to a biopolymer scaffold custom fit to the hemisection cavity.(25) The hemitranssection alone control group showed a BBB of ~7 (which is similar to the BBB score of sham injected animals in the McDonald paper), however the authors noted a significant improvement in BBB score in the scaffold plus NSCs groups to ~12. Animals that received scaffold alone improved to a mean BBB score of ~9. The authors postulate that the scaffold prevents scarring and cyst formation allowing axonal regrowth through the biopolymer pores. Scaffolds seeded with stem cells may result in more recovery secondary to neurotrophic factors secreted by the transplanted cells supporting regrowth. Indeed, histological evaluation of the spinal cords showed a higher proportion of GFAP positive astrocytes within the lesion epicenter in lesion control animals than in scaffold, or scaffold plus cells animals.

STROKE [4] RESOLUTION OF STROKE DEFICITS FOLLOWING CONTRALATERAL GRAFTS OF CONDITIONALLY IMMORTAL NEUROEPITHELIAL STEM CELLS26 STROKE 32, 1012-9, (2001).

Information

The authors investigated the potential of conditionally immortal NSC's to improve neurological function after transient middle cerebral artery occlusion (MCAo) in rats. Three study groups were used; 1) sham MCAo control, in which the left middle cerebral artery was exposed but not occluded, 2) MCAo + stem cell graft, in which the left MCAo was occluded for 60 minutes, followed 2-3 weeks later by injection of MHP36 NSC's into the contralateral somatosensory cortex and striatum. (3 μ l of MHP36 cells at 25,000/ μ l cells were injected into 8 targets along 4 needle tracts, for a total of ~600,000 transplanted cells per animal) 3) MCAo + sham graft, in which occlusion was followed by injection of an equal volume of vehicle into the same target sites. MHP36 is a murine stem cell line, which expresses the temperature sensitive tsA58 oncogene, allowing cells to propagate at low temperatures (33 degrees C), but resulting in differentiation into neurons and glia at 37 degrees C. Transplanted rats received cyclosporin A to prevent xenograft rejection. Behavioral evaluation was performed using the bilateral asymmetry test, water maze acquisition test, and rotation test. Animals were sacrificed for histological evaluation of stem cell distribution (immunohistochemistry for β -galactosidase), and stroke volume. Bilateral asymmetry test: Sham MCAo rats showed no paw preference, however MCAo + sham graft animals showed statistically significant and persistent sensorimotor deficiency in the right (contralateral) paw. Animals who received MHP36 grafts showed right paw impairment after MCAo, however this improved to the level of the control animals by 8 weeks post-transplantation. Water maze acquisition: All animals with MCAo strokes showed significant impairment in latency to find the underwater platform compared to sham-occlusion controls. There was no improvement seen in animals that received MHP36 grafts compared to sham stem cell grafts. Rotation: Animals with sham grafts showed a baseline asymmetric rotation to the right, whereas the stem cell transplanted and control rats showed no turning preference at baseline. In response to amphetamine, control animals as well as animals with MHP36 grafts showed no turning asymmetry, while animals with sham graft showed marked turning behavior to the left. Stroke Volume: Animals with MCAo, had stroke volumes that were 26% +/-4 of the total brain volume, whereas animals which received stem cell transplants had stroke volumes that were 16% +/-3 of the total brain volume. Stem cell transplantation had a significant effect on the stroke volume after MCAo. MHP36 cell distribution: β -galactosidase-positive cells were seen at the site of injection (contralateral striatum and somatosensory cortex), and were also seen in the corpus callosum and the residual contralateral striatum and parietal cortex. Additional immunohistochemistry to indicate whether cells had differentiated into neurons, astrocytes, or oligodendrocytes was not performed. The authors stated that cells showed the morphology of both neurons and glia.

Analysis

This study looked at behavioral recovery and stroke volume in an MCAo model in rats after transplantation of NSC's or injections of vehicle. The results suggest

that sensorimotor deficits, and rotational behavior due to MCAo strokes recover in animals with stem cell grafts and not in those with vehicle injection. However, stem cell transplantation appeared to have no benefit for spatial recognition tasks as seen with the water maze. Stroke volumes also decreased after stem cell injection. Transplanted cells can be seen in the contralateral brain at the sites of injection, but are also seen in the hemisphere ipsilateral to the stroke. NSC's have been shown before to have the ability to migrate long distances within the host brain. The authors postulate that the improvement in functional tests may be secondary to their assistance in neural reorganization and plasticity on the non-lesioned side of the brain as a compensation for functional loss on the lesioned side. Indeed most of the transplanted cells remained within the intact side of the brain. They also mention that cells that migrated to the stroke side may have reconstructed enough circuits to improve some behavioral functions.

GLIOMA [5] GENE THERAPY OF EXPERIMENTAL BRAIN TUMORS USING NEURAL PROGENITOR CELLS27 NAT MED 6, 447-50, (2000).

Information

One of the features that make glioblastomas incurable is their ability to infiltrate and migrate away from the tumor mass, which has made gene therapy ineffective due to difficulties in viral vector delivery. The authors investigated the possible use of neural progenitor cells (NPC) as a delivery mechanism for therapeutic molecules to tumor cells through their ability to migrate through normal brain along similar white matter pathways as gliomas. Interleukin 4 (IL-4) cDNA was transferred to NPCs derived from newborn C57BL6 mice. IL-4 production by the NPCs was tested for by ELISA and found to be 89ng x 10 cells per 48 hours. Control neural progenitor cells were transfected with the galactocerebrosidase (GALC) gene. GL261 glioma cells exposed to conditioned medium from NPC-IL-4 cells showed significant attenuation of growth as measured by incorporation of ^3H -thymidine. GL261 glioma cells were injected into syngeneic C57BL6 mice, alone, co-injected at a 1:1 ratio with NPC's expressing IL-4, or co-injected at a 1:1 ratio with NPCs expressing GALC. Mice injected with IL-4 NPCs lived significantly longer than control mice injected with glioma cells alone. Interestingly, mice injected with GALC NPCs also live longer than tumor alone, indicating that NPC's themselves have anti-tumor effect. These *in vivo* experiments were repeated in a model that more closely imitates human disease, in which tumors were allowed to grow for 5 days prior to injection of NPCs. Results in this model also showed significant survival prolongation in mice treated with IL-4 expressing NPCs. NPCs were pre-labeled with BrdU prior to injection to allow detection of cells *in situ*. NPC's were seen up to 20 days after injection within the tumor and at the tumor edges. *In Vivo* production of IL-4 was determined at 2 days and one month after injection of cells, which showed 50 pg/ml at 2 days and a decrease in the level of production by one month to ~6pg/ml.

Analysis

With this study, the authors have provided evidence that NPCs expressing IL-4 have a strong anti-tumor effect when injected into an intracranial model of

murine gliomas. Mice that received NPC-IL-4 lived significantly longer than mice without NPC transplantation. Interestingly, mice injected with NPCs expressing GALT, which has no anti-tumor effect, also lived longer indicating that NPCs have anti-tumor effects of their own. The ability of NPCs to migrate through brain along the same white matter tracts as glioma cells allows the delivery of therapeutic molecules directly to infiltrating cells. This ability of NSCs has been shown dramatically by others (28), in which NSCs expressing a therapeutic transgene were injected 1) into the tumor, 2) into a location distant to the tumor, but in the same hemisphere, 3) into the contralateral hemisphere from the tumor, and, 4) into the cerebral ventricle. Histological evaluation showed NSCs within the tumor mass in all 4 paradigms, demonstrating the extensive migratory ability of NSCs, and their tropism for tumor or injured CNS. In addition, NSCs appeared to be juxtaposed to tumor cells infiltrating away from the main tumor mass, indicating the ability of NSCs to track infiltrating cells along the same migratory pathways. These studies provide evidence that therapeutic molecules can be delivered to infiltrating tumors using the migratory abilities of NSCs. In addition, others have proposed that these NSCs can potentially help repair damaged areas within the brain, in contrast to other therapeutic modalities for gliomas such as chemotherapy and radiation.(29).

Synthesis

These papers have all tried to approach specific human neurological disorder that have poor prognoses and limited therapeutic options with novel therapies using stem cells. Different groups have used stem cells isolated by different mechanisms, but all have tried to capitalize on the multi-potent nature of the cells to develop into neural cells of all types. The advantage of stem cells over fetal brain tissue is the ability of stem cells to propagate in tissue culture in an undifferentiated state, to provide an unlimited source of cells for therapeutics. Previous studies using fetal brain tissue for these disorders required the use of multiple fetal brains to derive sufficient tissue to treat each patient. The ethical issues involved with that type of therapy, as well as the limited supply of tissue to translate into a therapy for millions of people has limited the success of such research. Stem cells can be propagated to provide an unlimited supply of cells after harvesting from one fetus or embryo. There are also ethical issues involved with this approach, which is why stem cell research has been debated on a national and international scale, however this topic is not within the scope of this article. These studies have demonstrated the immense potential of stem cell therapies for neurological diseases, however they are still preliminary. Further research is necessary to fully understand the biology of these cells and their therapeutic potential prior to advancing to clinical trials. However, these preliminary studies provide optimism that novel therapeutic modalities using stem cells may be beneficial to patients with neurological disease. These types of therapies will provide neurosurgical treatments for diseases that in the past have not been surgical in nature.

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