Cell Transplantation Therapy for Stroke

Tonya Bliss, PhD; Raphael Guzman, MD; Marcel Daadi, PhD; Gary K. Steinberg, MD, PhD

Abstract—No treatment currently exists to restore lost neurological function after stroke. A growing number of studies highlight the potential of stem cell transplantation as a novel therapeutic approach for stroke. In this review we summarize these studies, discuss potential mechanisms of action of the transplanted cells, and emphasize the need to determine parameters that are critical for transplantation success. (Stroke. 2007;38[part 2]:817-826.)

Key Words: clinical trials ■ neural stem/progenitor cells ■ stroke ■ transplantation parameters

Human stem cell transplantation therapy is well established for treating patients with hematopoietic and lymphoid cancers, other blood diseases, and some autoimmune disorders. Clinical stem cell transplant trials for other cancers, heart disease, diabetes, and pediatric traumatic brain injury are currently under way. Moreover, the first human neural stem cell clinical trial has recently been approved for Batten disease, a pediatric lysosomal storage disease that leads to neuronal loss and death.1 With such advances it becomes important to answer critical questions about the prospects of cell transplantation for stroke therapy.

Human Cells Used in Experimental Models of Stroke

Recent studies have highlighted the enormous potential of cell transplantation therapy for stroke. A variety of cell types derived from humans have been tested in experimental stroke models, and in many cases some index of behavioral function has been improved (Table 1). Human cells that have been used in these studies fall into 3 categories: (1) neural stem/progenitor cells (NPCs) cultured from fetal tissue; (2) immortalized neural cell lines; and (3) hematopoietic/endothelial progenitors and stromal cells isolated from bone marrow, umbilical cord blood, peripheral blood, or adipose tissue.

Neural Stem/Progenitor Cells

NPCs and immortalized NPCs grafted into the parenchyma (intracerebrally) surrounding the lesion or delivered intravenously survive, differentiate, and can enhance functional recovery (Table 1).2-6 With both routes of delivery, cells were found to home to the site of the lesion; this targeted migration may be mediated by injury-induced chemokines such as stromal-derived factor 1 and monocyte chemoattractant protein 1.7-9 Different preparations of NPCs give rise to varying proportions of neurons and glia after transplantation, but oligodendrocytes were rarely observed (Table 1). This variability in phenotypic fate is probably attributable to both cell intrinsic factors (the developmental potential of different fetal cell preparations) and extrinsic factors (the graft microenvironment) that can affect the outcome of fetal progenitor transplants. There is no obvious correlation between functional recovery and differentiation fate.

hNT Neurons

These postmitotic immature neurons are generated from the immortalized NT2 cell line derived from a human teratocarcinoma.10 These differentiated hNT cells (also known as NT2N cells or LBS neurons) maintain their neuronal phenotype both in vitro and in vivo for >1 year without reverting to a neoplastic state.11-13 hNT cells improve functional recovery when transplanted into the ischemia-damaged striatum of rats, in a dose-dependent manner14-16 (Table 1). Behavioral improvement persisted for up to 6 months after transplantation as long as the cells survived.15 However, survival of transplanted cells is not always correlated with functional recovery because we found no effect of these cells when transplanted into the ischemic cortex despite robust cell survival.17 This finding highlights the need to determine the parameters required for cell-enhanced functional recovery. These hNT neurons have been investigated in phase I and II clinical transplant trials of basal ganglia stroke (see below).

Bone Marrow, Umbilical Cord Blood, Peripheral Blood, and Adipose Tissue Cells

Human bone marrow cells (HBMC), human umbilical cord blood cells (HUCBC), peripheral blood progenitor cells, and adipose tissue mesenchymal stem cells have been reported by several groups to enhance functional recovery, whether delivered intracerebrally or intravenously (Table 1). HUCBC and HBMC are composed of many cell types including hematopoietic and endothelial stem/progenitor cells (CD34+), mesenchymal cells (CD34-), and immature lymphocytes and monocytes.18-21 It is not clear which of these cells are...
Because many behavior tests include an element of “motivation,” detecting a behavioral change in a given test does not necessarily mean that the test reflects a dysfunction associated with the site and extent of injury per se. Furthermore, a reversal of the behavioral effect by cell transplantation does not necessarily reflect an improvement in function.17

BBB indicates blood-brain barrier; CCAo, common carotid artery occlusion; CSA, cyclosporine A; dMCAo, distal middle cerebral artery occlusion, model of cortical ischemia; EBST, elevated body swing test; GFAP, marker of astrocytes and neural progenitors; IC, intracerebral; ICV, intracerebroventricular; IV, intravenous; MCAo, middle cerebral artery occlusion, primarily damages striatum and some cortex; MSCs, mesenchymal stem cells (also known as stromal cells); nestin, marker for NPCs, MSCs, and young endothelial cells; NA, not applicable; ND, not determined; NeuN and MAP2, neuronal markers; NSS, neurological severity score; VO, vessel occlusion; and vWF, endothelial cell marker.

*All studies were done in rat except where indicated as follows: (g), gerbil; (m), SCID mice.
important for functional recovery after stroke because different cell populations can enhance functional recovery (Table 1). Both HBMC and HUCBC target the ischemic border when delivered either intracerebrally or intravenously, and, as with NPCs, this is thought to be mediated by injury-induced chemokines. However, very few transplanted cells are found in the brain, even when delivered intracerebrally, and of these only a small percentage express neural markers. Given this and the controversy of whether these cells can really become neurons, it is unlikely that they act to replace the damaged tissue. It is more feasible that they secrete trophic factors that enhance endogenous mechanisms.
of brain repair.\textsuperscript{28,29} That functional recovery is found often with very few transplanted cells in the brain suggests that the cells may exert an acute but persistent effect on the brain before they die; intravenously administered cells may not even need to enter the brain to elicit an effect but rather act in the periphery to increase trophic factor expression in the brain.\textsuperscript{29} Recently, it has been demonstrated that the trophic effects of HBMC can be augmented by engineering them to overexpress trophic factors.\textsuperscript{30}

An advantage of a hematopoietic source of cells is that they avoid the ethical issues and tissue limitation associated with embryonic and fetal tissue. HBMC and peripheral blood stem cells also offer the potential of autologous transplants, negating the need for immunosuppression regimens. Another major advantage is that these cells are already used in the clinic for various malignant and nonmalignant disorders. Furthermore, the use of HUCBC for traumatic brain injury in children has just been approved (ClinicalTrials.gov Identifier: NCT00254722), this is the first clinical trial using these cells for a neurological disorder.

**Nonhuman NPCs in Experimental Stroke**
Surprisingly, few studies have used nonhuman NPCs, and most of these have used immortalized cells lines that may have unique properties not associated with “normal” NPCs.\textsuperscript{31} A comparison of the studies using nonhuman NPCs reveals that adult, fetal, and embryonic-derived NPCs can all elicit functional recovery after ischemia (Table 2). These cells exhibit robust migration to the ischemic area, even with contralateral implantation. In one study, grafting into the contralateral side was as effective in eliciting recovery as transplantation into the ischemic hemisphere.\textsuperscript{32} Stroke studies using embryonic stem cells highlight potential hazards of tumor formation.\textsuperscript{33}

**Potential Mechanisms of Transplanted Cell–Mediated Recovery**
Understanding how transplanted cells affect the brain, and vice versa, in model systems is important before proceeding to clinical trials. Various mechanisms may be responsible for the transplanted cell–mediated effect.

**Integration Into the Host Circuitry**
The attraction of using neural progenitor cells is their potential to replace lost circuitry and thus to have prolonged beneficial effects. However, evidence for this is limited.\textsuperscript{5,34} Expression of synaptic proteins by transplanted cells has been reported when rat NPCs were used in a model of global ischemia\textsuperscript{34} and with hNT neurons in a model of traumatic brain injury (not reported in the ischemic brain),\textsuperscript{35} indicating the potential of these cells to form synaptic contacts. Electron microscopy studies revealed that human NPCs formed synapses with host circuits in the ischemic brain.\textsuperscript{5} However, recovery occurred too early to be attributable to newly formed functional synapses,\textsuperscript{36,37} implying that additional (or alternative) mechanisms besides neural integration were involved. Specific neuronal subpopulations may be required for functional integration. For example, striatal neuronal progenitors (eg, from the lateral ganglionic eminence) may be necessary to repair damaged striatal circuitry\textsuperscript{38,39}; this has yet to be explored in the ischemic brain. The small numbers of transplanted cells surviving in the poststroke brain reported in some studies may pose a major problem if integration into the host circuitry is necessary for improved neurological outcome.

**Transplanted Cells Reduce Death of Host Cells**
Acute delivery of cells often reduces lesion size and inhibits apoptosis in the penumbra, suggesting that enhanced recovery results from neuroprotection (Table 1). A myriad of cell types elicit this effect. Common to all is the secretion of trophic factors, such as vascular endothelial growth factor, fibroblast growth factor, glial cell–derived neurotrophic factor, and brain-derived neurotrophic factor, that are likely to contribute to this neuroprotective mechanism.\textsuperscript{29,30,40,41}

**Induction of Host Brain Plasticity**
An increase in endogenous brain plasticity and motor re-mapping after ischemia is postulated to underlie the spontaneous recovery seen after a stroke.\textsuperscript{42–45} Such plasticity events include an increase in afferent and efferent connections between the site of injury and both adjacent and contralateral brain regions, restoration of local synaptic activity by synaptogenesis, and probably strengthening of existing synapses as well as activation of silent synapses. Cell transplantation may enhance these endogenous repair mechanisms. Human cord blood cells in the ischemic cortex increased sprouting of nerve fibers from the contralateral to the ischemic hemisphere.\textsuperscript{46} Shen et al\textsuperscript{47} reported increased synaptophysin expression in the penumbra after intravenous delivery of human bone marrow stromal cells. The potential of NPC grafts to alter plasticity has to date only been reported in models of epilepsy\textsuperscript{48}; however, data from our group show that NPCs increase synaptogenesis by neurons in vitro, and this is partly mediated by thrombospondins.

**Increased Neovascularization**
Increased vascularization in the penumbra within a few days after stroke is associated with neurological recovery and offers another potential target for cell therapy.\textsuperscript{49–53} Transplanted cell–induced blood vessel formation has been reported with bone marrow stromal cells,\textsuperscript{47,54} neural stem cells,\textsuperscript{55} and cells from human cord blood and peripheral blood.\textsuperscript{56,57} Direct incorporation of the transplanted cells into the new blood vessels has been observed in some cases. An indirect cell–induced effect on blood vessel formation is also likely; human bone marrow stromal cells promoted angiogenesis in the ischemic border by increasing endogenous levels of the angiogenic factor vascular endothelial growth factor.\textsuperscript{47,54} Transplanted cells have been reported to increase endogenous levels of other factors (brain-derived neurotrophic factor, stromal-derived factor-1, and fibroblast growth factor) that could induce proliferation of existing vascular endothelial cells (angiogenesis) and mobilization with homing of endogenous endothelial progenitors (vasculogenesis).

**Attenuation of Inflammation**
An intriguing potential repair mechanism is the ability of transplanted cells to attenuate the stroke-induced inflamma-
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Stroke Model*</th>
<th>Time of Delivery After Stroke</th>
<th>Route of Delivery</th>
<th>Effect on Lesion Size</th>
<th>Survival</th>
<th>Phenotype of Cells in Brain</th>
<th>Functional Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHP3690</td>
<td>60-min MCAo</td>
<td>2 wk</td>
<td>IC: striatum + cortex; ICV: bilateral</td>
<td>ND</td>
<td>No significant difference in survival between ipsilateral and contralateral grafts at 2 wk after transplantation</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>MHP3691</td>
<td>60-min MCAo</td>
<td>2–3 wk</td>
<td>IC: contralateral striatum + cortex</td>
<td>Decreased (at 11 mo)</td>
<td>ND</td>
<td>ND</td>
<td>Recovery on sticky tape test (6–18 wk) and rotation bias test (38–45 wk), not MWM (26–29 wk)</td>
</tr>
<tr>
<td>MHP3692</td>
<td>2-VO global ischemia (m)</td>
<td>3 d</td>
<td>IC: ipsilateral striatum</td>
<td>Decreased (at 1 mo)</td>
<td>ND</td>
<td>50% neurons</td>
<td>Both cell lines induced similar recovery on MWM</td>
</tr>
<tr>
<td>MHP36 and E19 CA1 primary suspension51</td>
<td>4-VO 15 min</td>
<td>2–3 wk</td>
<td>Bilateral into hippocampus CA1</td>
<td>None</td>
<td>MHP36 mostly in CA1 (at 4 wk); CA1 primary cells aggregated outside CA1</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>C17.2 (immortalized neural precursor cell line from neonatal mouse cerebellum)52</td>
<td>dMCAo (m)</td>
<td>Immediately after stroke</td>
<td>IC: contralateral frontal lobe; ICV: contralateral</td>
<td>ND</td>
<td>With both delivery routes cells crossed the midline but only in stroke and not control animals</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>NPCs from adult rat SVZ53</td>
<td>Embolic MCAo</td>
<td>2 d</td>
<td>Cisterna magna</td>
<td>ND</td>
<td>ND; cells only found on ischemic side</td>
<td>ND</td>
<td>Recovery on foot fault and sticky tape tests</td>
</tr>
<tr>
<td>NPCs from adult rat hippocampus54</td>
<td>4-VO 15 min</td>
<td>2 wk</td>
<td>Bilateral dorsal hippocampus</td>
<td>ND</td>
<td>In CA1 (1–3%) and corpus callosum</td>
<td>ND</td>
<td>Partial improvement in MWM if &gt;120 grafted cells were neurons</td>
</tr>
<tr>
<td>NPCs from E14 rat hippocampus overexpressing VEGF55</td>
<td>120-min MCAo</td>
<td>3 d</td>
<td>IC: ipsilateral striatum</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>NPCs and VEGF-transfected NPCs both improved NSS compared with vehicle treatment; effect seen earlier in the VEGF group (2–12 wk) than in the NPC group (8–12 wk)</td>
</tr>
<tr>
<td>NPCs from E15 mouse cortex56</td>
<td>60-min MCAo</td>
<td>24 h</td>
<td>IC: ipsilateral striatum; ICV: ipsilateral; IV</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Cells delivered by all routes migrated to the ischemic lesion IC-&gt;IV</td>
</tr>
<tr>
<td>Mouse ES cells (D3) expressing GFP57</td>
<td>60-min MCAo</td>
<td>2 wk</td>
<td>Contralateral corpus callosum and striatum</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Mouse ES cells (D3) expressing GFP58 (m + r)</td>
<td>60-min MCAo</td>
<td>2 wk</td>
<td>Contralateral cortex and striatum</td>
<td>ND</td>
<td>ND</td>
<td>Some are neurons</td>
<td>ND</td>
</tr>
<tr>
<td>Mouse ES cells59</td>
<td>30-min MCAo (m)</td>
<td>2 d</td>
<td>Ipsilateral striatum</td>
<td>No significant difference at 2 and 4 wk</td>
<td>ND</td>
<td>60% NeuN, 40% TuJ1, 22% GFAP, 0.4% GalC</td>
<td>ND</td>
</tr>
<tr>
<td>Primate ES cells60</td>
<td>30-min MCAo (m)</td>
<td>1 d</td>
<td>Ipsilateral striatum</td>
<td>No change at 28 d</td>
<td>ND</td>
<td>After 28 d: 62% HuC (immature neurons), 60% HuD (mature neurons), 1.4 % GFAP</td>
<td>ND</td>
</tr>
</tbody>
</table>

*dMCAo indicates distal middle cerebral artery occlusion, model of cortical ischemia; GalC, oligodendrocyte marker; GFAP, marker of astrocytes and neural progenitors; IC, intracerebral; ICV, intraventricular; IV, intravenous; MCAo, middle cerebral artery occlusion, primarily damages striatum and some cortex; MSCs, mesenchymal stem cells (also known as stromal cells); MWM, Morris water maze; ND, not determined; NeuN and MAP2, neuronal markers; NSS, neurological severity score; TuJ1, immature neuronal marker; IV, vessel occlusion. For a summary of earlier transplantation studies in models of cerebral ischemia, see Borlongan et al.99

*All studies were done in rat except where indicated as follows: (m), mouse; (m+r), mouse and rat.
Recruitment of Endogenous Progenitors

Endogenous neurogenesis is increased after a stroke. The function of this has yet to be determined but may signify a natural repair mechanism of the brain that could potentially be further enhanced by transplanted cells. There is precedence for this with cord blood cells and bone marrow cells. In addition to local effects on the damaged tissue, transplanted cells could potentially recruit different progenitor cell types from other tissues. As mentioned above, they could mobilize endogenous endothelial progenitors into the circulation to enhance vascularization. Whether cell transplantation enhances endogenous hematopoietic or mesenchymal cell mobilization after ischemia has yet to be determined.

With all the aforementioned mechanisms, whether the phenomenon measured is a cause or a secondary effect of cell-enhanced functional recovery needs to be determined.

Clinical Trials of Cell Transplantation for Stroke Treatment

hNT cells

hNT cells are the only human cells that have been tested in clinical trials for patients with stroke. In the phase I trial, the 12 chronic basal ganglia stroke patients (aged 44 to 74 years), who had stable motor deficits and experienced a stroke 6 months to 4.5 years before implantation, showed no cell-related adverse effects even 5 years after the cell transplantation. These patients received immunosuppression treatment for only 8 weeks after surgery. Autopsy on 1 patient revealed that some hNT cells were still detectable in the brain at 27 months after implantation, suggesting that the grafts survived without continued immunosuppression. This is in contrast to the rodent study in which the cells died without immunosuppression treatment. Furthermore, positron emission tomography (PET) scans at 6 months after implantation showed high metabolic activity in the graft area, suggesting that the grafts survived without continued immunosuppression. This is in contrast to the rodent study in which the cells died without immunosuppression treatment. Additionally, PET fluorodeoxyglucose activity.

In a phase II trial, 18 patients with stable deficits 1 to 6 years after basal ganglia stroke were randomized to stereotactic transplantation (n=14, 5, or 10 million cells) or control (n=4). All patients received 8 weeks of constraint therapy. Six of 14 transplanted patients showed improvement on the European Stroke Scale, and this correlated with increased PET fluorodeoxyglucose activity.

Timing of Transplantation

The optimal timing of transplantation after a stroke is not known. The brain environment changes dramatically over time after ischemia. In the acute phase there is an increase in excitatory amino acid release, peri-infarct depolarization, and reactive oxygen species release. This is followed by an inflammatory/immune response and cell death, which, in the penumbra, can last up to several weeks. Brain repair and plasticity after the acute phase take place over several weeks to months. The optimal timing of delivery will depend on the cell type used and their mechanism of action. If a treatment strategy focuses on neuroprotective mechanisms, acute delivery of the cells will be critical. If the cells act to enhance endogenous repair mechanisms (eg, plasticity, angiogenesis, and neurogenesis) or require these events in order to survive and integrate, then early delivery would be pertinent because these events are most prevalent in the first 2 to 3 weeks after ischemia. If cell survival is important, then transplanting late, after inflammation has subsided, could be beneficial. Given the significant role of astrocytes in the neurogenic niche, it will be of interest to determine how ischemia influences the temporal and spatial expression profile of astrocytic-derived factors such as Wnt and bone morphogenetic protein inhibitors (eg, Noggin, neurogenesin-1), which are thought to promote adult endogenous neurogenesis; such environmental cues could be advantageous for transplanted neural precursor cells. A systematic analysis of transplanta-
tion timing and its effect on functional recovery has not been done. The literature reports a wide range of stroke-to-transplantation intervals. Many studies demonstrating functional recovery report transplantation within the first 3 days after ischemia (Tables 1 and 2). However, cell-enhanced recovery has been reported with chronic delivery of cells even at 1 month after ischemia.14–16,24 The optimal approach in the clinical setting has yet to be defined.

Lesion Location and Size
Lesion location and size will be important factors in determining which patients are suitable for transplantation therapy. To date, most experimental studies showing cell-enhanced recovery used a stroke model that damages the striatum (with some damage to the cortex), and the cells are often delivered into the striatum (Tables 1 and 2). Only a few studies have investigated cell therapy for lesions that primarily damage the cortex, and most of these have used primary fetal tissue blocks, with varying efficacy.76–78 A similar dichotomy is found with the few studies grafting cell suspensions into the cortex: HBMC and peripheral blood CD34+ cells enhanced recovery on several tests57,79; NPCs improved function but only if combined with housing in an enriched environment80; we found very little effect of hNT cells on a battery of behavioral tests despite impressive graft survival and neurite extension.17 These data suggest that recovery from cortical damage may be more complex than from striatal damage. However, a direct comparison between the 2 types of lesions, transplanting the same cells at the same time point and using the same behavioral tests, is required before a conclusive statement can be made. It may simply be that the infarct associated with cortical stroke models is too large and too many essential connections are severed to make repair feasible. Precise anatomic location of the lesion and its functional implication, as well as lesion size, will be critical determinants to define the target populations for clinical trials.

Route and Site of Cell Delivery
Studies have reported functional recovery with intracerebral, intracerebroventricular, and intravenous delivery of cells (Tables 1 and 2). A comparison of delivery methods determined that all routes resulted in cells targeting the lesion, but more cells were found at the lesion with intracerebral delivery, followed by intracerebroventricular and then intravenous delivery.81 With intracerebral delivery, more cells are found near the lesion with ipsilesional versus contralateral grafts, although both graft sites resulted in a similar extent of recovery near the lesion with ipsilesional versus contralateral grafts,29 In 1 study, intravenous delivery of HUCBC at 24 hours was more beneficial than intracerebral delivery,82 although the opposite was found for bone marrow cells.83 The route of delivery may also influence the type of recovery; intracerebral delivery of MHP36 cells only enhanced sensorimotor function, whereas intracerebroventricular delivery only affected learning and memory.32 The optimum route of delivery will be dependent on the cell type and the mechanism of action.

In Vivo Monitoring of Repair Progress in Patients
Clinical studies will require noninvasive methods to monitor the transplanted cells. PET scanning evaluates the metabolic activity at the site of cell transplantation but is unable to identify precise anatomic location or cell migration. Tagging the cells with nanoparticles (superparamagnetic iron oxide particles [SPIO]) allows them to be monitored with the use of MRI.84,85 Studies from our group show that SPIO labeling allows in vivo cell tracking over several weeks and does not obviously affect migration, integration, and differentiation of human neural stem cells. Although SPIO labeling and MRI will answer questions on anatomic location and migratory characteristics of the transplanted cells, functional imaging studies including PET (to monitor the metabolic activity), perfusion studies (to monitor potential angiogenesis and neovascularization), functional MRI (to monitor cerebral plasticity) and diffusion-tensor imaging fractional anisotropy (to evaluate fiber tract integrity) will help to answer questions on repair mechanisms of the transplanted cells. Because of the limited sensitivity and specificity inherent to all these methods, multimodality imaging will be crucial in the post-transplantation patient assessment. The information gathered in this manner will increase the value of clinical trials and, it is hoped, will yield predictors of functional outcome.

Conclusions
Cell transplantation therapy for stroke holds great promise. However, many fundamental questions related to the optimal candidate (including the patient age, etiology, anatomic location and size of the infarct, and medical history), the best cell type, the number and concentration of cells, the timing of surgery, the route and site of delivery, and the need for immunosuppression remain to be answered. To this end, some standardization of the basic research, especially for behavior, is needed so that direct comparisons can be made between studies. Furthermore, longer-term studies are required to determine whether the cell-enhanced recovery is sustained and also to determine the tumorigenic potential of the cells. Tumors could possibly arise directly by transformation of the transplanted cells or indirectly by the induction of endogenous tumors through secretion of factors by the transplanted cells. Other challenges include ensuring appropriate characterization, manufacturing, and quality control of transplanted cells and rigorous testing of viral and adventitious agents. Clearly, more research is needed to understand the bidirectional interaction between the transplanted cells and the host to optimize the chances of success before proceeding to the clinic. Collaboration between neuroscientists, neurosurgeons, and neurologists is required to translate cell transplantation therapy to the clinic in a timely but safe and effective manner so that the remarkable potential already shown for cell transplantation to aid recovery from experimental stroke can become a reality for the patient.

Acknowledgments
We wish to thank Dr Bruce Schaar for critical reading of the manuscript and Dr Tim Schallert for helpful suggestions.
Sources of Funding

Dr Steinberg is funded by National Institutes of Health, National Institute of Neurological Disorders and Stroke grants 2R01 NS27292 and 2P01 NS37520, Russell and Elizabeth Siegelman, the William Randolph Hearst Foundation, and Bernard and Ronni Lacroute. Dr Guzman is supported by Swiss National Science Foundation grants PPBBE-104450 and SSMSB-1194/PASMA-108940.

Disclosures

None.

References


59. Bliss et al Cell Transplantation Therapy for Stroke 825


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Stroke. 2007;38:817-826
doi: 10.1161/01.STR.0000247888.25985.62
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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