

DE NOVO NEUROGENESIS AND ACUTE STROKE: ARE EXOGENOUS STEM CELLS REALLY NECESSARY?

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Received, March 20, 2003.

Accepted, August 28, 2003.

RECENT STUDIES DOCUMENTING the phenomenon of de novo neurogenesis within the adult brain have propelled this area of research to the forefront of neuroscience investigations and stroke pathogenesis and treatment. Traditional theories have suggested that the central nervous system is incapable of neural regeneration; hence the emergence of the field of stem cell biology as a discipline devoted to uncovering novel forms of neural repair. However, several recent experimental observations have shown that the adult brain is capable of ongoing neurogenesis in discrete regions of the uninjured brain and additional forms of endogenous neural regeneration in the presence of an inciting event (induction neurogenesis). Induction neurogenesis has the potential for providing new insights into the cause and treatment of acute stroke syndromes.

KEY WORDS: Cellular transplantation, De novo neurogenesis, Induction neurogenesis, Neural stem cells, Stroke

Neurosurgery 54:150-156, 2004

DOI: 10.1227/01.NEU.0000097515.27930.5E

www.neurosurgery-online.com

Stroke is one of the most common causes of death and disability in adults in industrial societies, with approximately 200 new strokes per 100,000 adults per year (13). In the United States, the incidence of stroke is approximately 750,000 cases per year; it is the third leading cause of death and the most common cause of disability among adults (40). Attempts to decrease stroke incidence through control of vascular risk factors have been counterbalanced by the cumulative effects of an aging population. Recent efforts to develop effective therapeutic approaches have targeted acute stroke with typically short perinfarction time windows for institution of effective therapeutic modalities, in particular, acute thrombolysis.

Current treatment paradigms with intra-arterial and intravenous thrombolytics have revolutionized the management of acute stroke in a select subgroup of patients. However, only certain patients are eligible for thrombolysis, whereas others experience persistent cerebrovascular occlusion with further progression of ischemia and its associated progressive neurological deficits. In fact, with the exception of thrombolytic therapy, modern clinical management is based primarily on supportive care. Experimental studies in animals have focused on a number of molecular

therapies that target different stages of the ischemic process. Recent advances in molecular biology have allowed new approaches to enhance neuronal regeneration through the use of gene therapy, neurotrophic factors and associated cytokines, and more recently, neural stem cells (NSCs).

For several years, there has been a growing interest in the therapeutic potential of NSCs and more lineage-restricted progenitors for the remediation of a spectrum of central nervous system disorders. The original cells of an embryo, or stem cells, are at the earliest stage of development and thus can form literally any kind of cell (cardiac, gastrointestinal, etc.), whereas NSCs are restricted to becoming nervous system cells. As development progresses, NSCs that started out with unlimited potential have their fate determined by their surrounding environment and signaling pathways. As these NSCs undergo further differentiation into specific types of mature, non-dividing cells, they form neural progenitors until they reach their final form as a neuron, astrocyte, or oligodendrocyte.

NSCs are present during embryonic and postnatal development and persist during adult life within paramedian generative zones present throughout the neuraxis. NSCs are defined by their ability to 1) regenerate exact

CELLULAR TRANSPLANTATION

copies of themselves (self-renewal) during the initial phase of stem cell expansion (symmetric cell division) and later during neural lineage elaboration (asymmetric cell division); 2) undergo exponential cell growth and division; 3) give rise to all of the mature neurons and glia of the region of stem cell origin (multipotency); and 4) undergo neuronal and glial lineage commitment, migration, and progressive cellular maturation in response to a spectrum of injury signals. NSCs can be isolated, grown, and “programmed” under specific tissue culture conditions and subsequently engrafted into the recipient brain and there successfully integrate into the recipient area. The biological properties of NSCs provide them with the innate potential to integrate into the existing neural circuitry after transplantation in a developmentally appropriate sequence that endows their progeny with mature electrophysiological properties.

During the past decade, cellular transplantation for the treatment of neurodegenerative disorders has become an exciting focus of neuroscience research. Cell replacement strategies to restore function in neurodegenerative diseases such as Parkinson’s disease are based on intracerebral transplantation of primary fetal cells, progenitor cells predifferentiated *in vitro*, and NSCs (9). The majority of the work in the field of applied NSC biology has been in the area of neurodegeneration, with a limited number of investigations performed in the area of stroke (11, 34, 37, 39) and spinal cord injury. As the success of *in vitro* and *in vivo* methods for targeting neurodegenerative disorders improved, treatment paradigms were developed for acute stroke based on engrafting NSCs to replace dying or dysfunctional cells within the ischemic cortex.

Traditional thinking has taught that the adult brain is incapable of significant self-repair or regeneration, in contrast to the exuberant reparative processes seen in other tissues, such as skin and liver (10). In these other organ systems, dead cells are replaced by identical cell types after the proliferation and differentiation of nearby cells or resident stem cells. Thus, cellular transplantation rather than induction of nascent stem and progenitor precursors of the target cells seemed to be the most viable option for stroke therapy. However, emerging evidence from a number of studies has now convincingly demonstrated that NSCs and progenitor cells do exist within the adult mammalian brain with the ability to produce new neurons and glia in response to a variety of environmental perturbations. The elaboration of neurons and glia from existing precursors is known as induction neurogenesis and is based on recovering the latent regenerative potential of stem and progenitor cells in response to cues emanating from damaged and remote neurons and their glial supporting cells. Although NSCs and progenitor cells have been promoted as the most effective method for treatment of a broad spectrum of neurological disorders, cell transplantation may not be an indispensable and effective strategy in the treatment of acute stroke. The purpose of this review is to describe possible innovative therapies based on induction neurogenesis and its various modifications as an attractive alternative to the use of direct cellular transplantation with NSCs or progenitor cells.

One of the pioneering studies using an exogenous cell line for regeneration in areas of the central nervous system damaged by stroke was performed by Kleppner et al. (21). Their cells were derived from a teratocarcinoma cell line, Ntera 2/cl.D1 (NT2), expanded in cell culture, and differentiated into pure postmitotic human neuronal cells (LBS-Neurons, Layton BioScience, Sunnyvale, CA) upon treatment with retinoic acid. In a middle cerebral artery (MCA) occlusion model of stroke in rats, injection of these cells into the area of ischemia resulted in a partial restoration of behavioral and motor function (11). Follow-up studies in these animals at 14 months showed no toxicity or tumor formation (21). Thereafter, a human clinical trial included 12 patients with basal ganglia stroke who, from 6 months to 6 years after stroke onset, received stereotactic injections of hNT cells (LBS-Neurons) into their ischemic brain regions. The outcome of this study revealed an increase in the European Stroke Scale scores, thus demonstrating that neuronal cell transplantation can be a therapeutic option for stroke patients with a motor deficit (22). However, a follow-up study using serial metabolic brain imaging with [¹⁸F]fluorodeoxyglucose positron emission tomography that was obtained both before and after implantation of these hNT cell-derived neurons showed a 10% increase in functional activity at 6 months, with a return to baseline at 12 months.

Although these cells showed promise, hNT cells are not true stem cells and have been criticized for their difficulty in provenance for large-scale clinical use. Initial reports lacked convincing evidence on whether these cells actually integrated into the damaged parenchyma to form functionally significant neural network connections within the existing cytoarchitecture or how they contributed to behavioral recovery. However, a recent report using hNT cell line neurons transplanted into a rat model of complete spinal cord contusion with loss of motor evoked potentials proved otherwise (36). In that study, rats underwent immediate and delayed (2 wk) transplantation, with significant functional recovery demonstrated by return of motor evoked potentials and some improvement in motor function.

Snyder et al. (37) developed a multipotent NSC line (C17.2) derived from individual murine cerebellar external granular layer progenitor cells transduced with a *v-myc* oncogene. The engrafted cells, identified by lacZ expression and polymerase chain reaction-mediated detection of a unique nucleotide sequence arrangement, could be identified in animal studies up to 22 months after engraftment. Initial results showed that 5% of engrafted NSCs on the injured side differentiated into neurons, with no new neurons seen in the uninjured cortex (34). This study suggested that immortalized multipotent NSCs may represent an additional source of exogenous cells to participate in neural repair in acute stroke syndromes (31, 34, 37, 38).

Additional studies have used NSCs in both rat (39) and murine (31) models of stroke, engrafted both before and after

induction of ischemia, and engrafted ipsilateral as well as contralateral to the lesion site (38, 39). Previous studies suggested that NSCs would not survive directly in the area of ischemia. Therefore, the side contralateral to the lesion was chosen to avoid exposing the cells to the poorly vascularized, inflammatory milieu of the progressive ischemic lesion. Furthermore, it has been postulated that NSCs would cross hemispheres through white matter tracks and proliferate adjacent to or within areas of ischemia; however, these issues are still being investigated.

Although NSC engraftment in stroke has shown initial therapeutic promise, there are numerous technical, political, and ethical issues surrounding the use of these cells. An obvious advantage of de novo neurogenesis over cell transplantation is that there is no need for an external source of cells, whether embryonic, derived from nonhuman species, or cells grown in tissue culture. Xenotransplantation from other animals carries the risk of introducing diseases into humans, which is obviated with de novo neurogenesis. In addition, cultured cells need to be immortalized by traditional or conditional oncogenes, thereby increasing the risk of tumorigenesis once they are transplanted into the host.

INDUCTION NEUROGENESIS

What Is Induction Neurogenesis?

Altman et al. were the first to show that de novo neurogenesis occurs constitutively in the hippocampus (4) and olfactory bulb (3) of the adult mammalian brain. Active neural precursors in adult brain are restricted primarily to two regions: the subventricular zone (SVZ) lining the lateral ventricles and the subgranular zone of the dentate gyrus (15), with additional multipotent progenitors residing in the cerebral cortex remote from paramedian generative zones (28, 32, 35, 42, 43). After constitutive neurogenesis was identified in specific regions of the adult brain, Reynolds and Weiss (35) showed that precursor cells isolated from the adult forebrain could differentiate into neurons and glia in vitro.

Once neurogenesis was detected and proven to occur, it was found that such causes of neuronal death as cerebral ischemia, epileptic seizures, and trauma are accompanied by the induction of neurogenesis in the subgranular zone (5, 7, 26, 33) and SVZ (20, 44). In fact, various soluble and cell-associated injury signals can activate regional stem cell subpopulations to selectively supply the appropriate complement of neurons and glia lost after cortical injury. Novel strategies aimed at inducing de novo neurogenesis in ischemic cerebral cortex from uninjured endogenous NSC pools may permit the reconstitution of neural network connections and associated behavioral recovery not previously attainable by use of traditional cellular transplantation approaches.

Where Do Endogenous Neural Progenitors Originate?

Using a model of global ischemia, Nakatomi et al. (29) demonstrated a significant increase in the number of NeuN⁺

(a marker for new neurons) neurons that originated from posterior periventricular zones and the hippocampal parenchyma. Although hippocampal dentate granule neurons turn over continuously in adults, projection neurons of the hippocampus proper do not. Arvidsson et al. (5) induced transient MCA ischemia in adult rats and showed that there was a marked increase of cell proliferation in the SVZ. It was concluded that new neurons and nascent neuroblasts, perhaps already present before the ischemic insult, had the potential to migrate into the area of the damaged striatum. However, an important observation was that there were no new neurons present within the parietal cortex. Thus, an intriguing aspect of induction neurogenesis is to control the areas in which cells develop and to which they migrate in the area of ischemia. In another study using a rat MCA occlusion model, Li et al. (25) showed that ependymal, subependymal, and choroid plexus cells are potential neural precursors in the adult mammalian brain.

Mechanisms for Neurogenesis

One mechanism for de novo neurogenesis has been related to the *N*-methyl-D-aspartate (NMDA) receptor. Arvidsson et al. (6) occluded the MCA in adult rats for either 30 minutes or 2 hours and evaluated the presence of de novo neurogenesis in the dentate gyrus. There was enhanced neurogenesis in the ipsilateral dentate granule cell layer and subgranular zone in those animals after 2 hours of MCA occlusion. The magnitude of neurogenesis was not correlated with the degree of cortical damage, and systemic administration of an NMDA receptor blocker suppressed neurogenesis in those animals with 2 hours of occlusion. The authors concluded that neurogenesis in the rat stroke model may be mediated by a glutamatergic mechanism acting, at least in part, through the NMDA receptor.

Therapies Directed at Enhancing Neurogenesis

After the onset of ischemia, regardless of cause, reperfusion occurs, with an ensuing cascade of both cellular and molecular events associated with inflammation, excitotoxicity, nitric oxide production, free radical damage, and apoptosis. Inflammatory cytokines, primarily interleukin (IL)-1 β and tumor necrosis factor, are released by microglia, astrocytes, endothelial cells, and neurons. Other inflammatory and immunomodulatory cytokines released in response to ischemic injury include IL-1, IL-6, tumor necrosis factor- α , transforming growth factor- β , and IL-10. Multiple inhibitory cues have been identified after vascular injury, including formation of glial scars by astrocytes, reduced trophic factor support for neurons, and breakdown products of myelin that inhibit regenerating axons.

Inhibition of axonal regeneration by factors released from myelin breakdown is one of a number of factors preventing recovery after neuronal injury. Inhibitors of neurite growth, such as Nogo A, myelin-associated glycoprotein, and oligodendrocyte-myelin glycoprotein, have all been identified

as being released after injury and before scar formation (14). These inhibitors are found in myelin membranes immediately adjacent to the axon, providing an optimal location to mediate axon-glia interactions. More importantly, they all bind to the Nogo receptor, inhibiting axonal outgrowth and additional remyelination and preventing subsequent neuronal recovery (23). Blockade of Nogo receptor may allow for an enhanced regenerative response after neuronal damage, further augmenting the mechanisms of neurogenesis (23).

Neurogenesis Enhanced by Gene Therapy

Although injury-mediated neurogenesis seems to be a *bona fide* mechanism for neural repair, recent investigations have attempted to enhance this response through gene therapy. The intraventricular delivery of and ependymal infection by viral vectors encoding neurotrophic agents may be a feasible strategy for inducing and enhancing neurogenesis from resident stem and progenitor cells within the adult brain. Recent studies have shown that a single injection of adenoviral brain-derived neurotrophic factor into the lateral ventricle substantially augmented the recruitment of new neurons into both neurogenic and non-neurogenic sites in the adult rat brain (8). Abe et al. (2) stereotactically injected an adenoviral vector encoding LacZ directly into ischemic or reperfused cerebral cortex to determine subsequent cellular growth factor expression profiles. Growth factor expression was dramatic between 7 and 21 days; the majority of expressing cells were composed of resident neurons and glia. Additional studies have used glia-derived neurotrophic factor (GDNF), a distant member of the transforming growth factor- β superfamily, which is a potent neurotrophic factor for promoting survival of cells, including brain tissue, under ischemic conditions (1). Iwai et al. (18) injected an adenoviral vector encoding GDNF (Ad-GDNF) directly into the rodent cerebral cortex after induction of ischemia. The viral vector was injected 1 day before temporary (90 min) occlusion of the MCA and showed a reduction in stroke volume compared with control vector (Ad-LacZ). Yagi et al. (41) administered Ad-GDNF or control vector to gerbils 2 days before they underwent transient (5 min) bilateral common carotid artery occlusion using aneurysm clips to produce forebrain ischemia. Treatment with Ad-GDNF significantly attenuated the loss of hippocampal CA1 pyramidal neurons from 2 to 7 days after ischemia compared with controls, and it was concluded that Ad-GDNF may have prevented delayed neuronal death as a result of stroke.

One recent study has investigated the use of intraventricular GDNF in human subjects. A multicenter, randomized, double-blind, placebo-controlled, sequential cohort study compared the effects of monthly intraventricular administration of placebo versus escalating doses of GDNF (25–4000 μg) for 8 months in 50 subjects with Parkinson's disease (30). Results showed that functional scores were not improved by GDNF at any dose and that there were serious common side effects, such as weight loss, nausea, anorexia, vomiting, hyponatremia, and paresthesias, up to several days after injections.

Neurogenesis Enhanced by Growth Factors

Fibroblast growth factor-2 and epidermal growth factor (EGF) act as mitogens for adult stem and progenitor cells (12, 24). The infusion of EGF into the lateral ventricle of adult mouse forebrain for 6 consecutive days resulted in a substantial increase in cellular proliferation and in the total number of subependymal cells (12). These cells migrated away from the lateral ventricle walls adjacent to the parenchyma. EGF may act directly as a proliferation, survival, and migration factor for these subependymal stem and neural progenitor cells. Nakatomi et al. (29) infused the intraventricular growth factors fibroblast growth factor-2 and EGF for 3 days after induction of global ischemia, which resulted in a 40% replacement by endogenous neural precursors. Furthermore, the observation of enhanced neurogenesis confirmed the mitogenic effects of these growth factors on the endogenous progenitors that migrated into the area of ischemic cell death within the non-neurogenic area of the hippocampus.

A special form of EGF, heparin-binding EGF, is found in cerebral neurons, and its expression is increased after hypoxic or ischemic injury stimulating neurogenesis (19). Intraventricular injections of heparin-binding EGF caused an increase in neurogenesis in the SVZ and subgranular zone of the dentate gyrus. Mehler and Gokhan (28) isolated distinct populations of EGF- and basic fibroblast growth factor-responsive multipotent progenitors from the postnatal mammalian cerebral cortex distinct from the SVZ. These latter observations suggest that multiple pools of NSCs and progenitor cells exist that may contribute to *de novo* neurogenesis in response to parenchymal injury signals. These cumulative studies also demonstrate that neural progenitor cells are under strict environmental controls for graded forms of neural development and possibly neuroregenerative responses mandated by specific cytokines and growth factor response profiles.

Migration and Replacement of Newly Formed Neural Progenitors

Once *de novo* neurogenesis has occurred, nascent neuroblasts need to migrate to the site of injury and to replace neurons that have died, suggesting that robust regenerative responses do not occur *in vivo*. However, Magavi et al. (27) found that after focal cortical ablation, a small number of new neurons were observed to be extending processes to the original target sites in the thalamus. The neuronal reparative response was selective. Only targeted neurons that were destroyed underwent cellular replacement, without affecting cells within the surrounding tissue. After infusion of growth factors in a rat MCA occlusion model, Nakatomi et al. (29) showed by triple staining with bromodeoxyuridine, microtubule-associated protein-2, and synaptophysin that newly generated neurons (bromodeoxyuridine) exhibited exuberant dendritogenesis, as judged by staining for microtubule-associated protein-2, and formed synaptic connections with multiple synapsin I⁺ presynaptic fibers. In the same study, the investigators also showed the presence of a significant synaptic response, as judged by the presence of action potentials and specific forms of synaptic plasticity, in the growth factor-

treated group compared with nontreated ischemic cortex, although these physiological signatures were dampened compared with analogous responses from normal cortex.

In a rat model of transient MCA ischemia, Arvidsson et al. (5) showed that newly generated neurons were distributed in a gradient from the SVZ to the parenchyma, with half of these cells located 0.5 mm lateral to the SVZ and additional cells scattered up to 2 mm away. These neurons were also found to develop striatum-specific characteristics. Magavi et al. (27) induced synchronous apoptotic degeneration of corticothalamic neurons in layer VI of the anterior cortex of adult mice and examined the fates of dividing cells within the cortex. Cells induced by neurogenesis expressed NeuN (a mature neuronal marker) in areas of cortex with targeted apoptosis and survived for 28 weeks. They also showed that neurons have the capacity to form long-distance corticothalamic connections. Other investigations, in a primate model, have shown the presence of new neurons up to 11 mm outside of the olfactory bulb and dentate gyrus. However, in these studies, it was not clear whether new neurons had incorporated into local neuronal networks (16).

Imaging and Neurogenesis

One method of monitoring NSC proliferation and migration is the use of high-field magnetic resonance imaging (MRI) with an appropriate contrast agent. Hoehn et al. (17) induced focal cerebral ischemia 2 weeks before transplantation of embryonic stem cells that expressed green fluorescent protein and were labeled with an MRI contrast agent. The cells were injected contralateral to the stroke in two areas and followed with serial MRI (7 T). This study showed that cells migrated along the corpus callosum to the ventricular walls and populated the border zone of the ischemic cortex. This confirmed the fact that stem cells have migrational dynamics that favor the area of infarction. MRI thus has the potential to serve as a powerful and dynamic tool to follow NSC proliferation, migration, survival, and differentiation in vivo models of cerebral ischemia.

CONCLUSIONS

Induction neurogenesis is a new and promising therapeutic paradigm for the treatment of acute stroke. Although the first clinical trial for stroke in humans was based on an exogenous transplanted cell line, there are immense political, ethical, and clinical obstacles associated with cellular transplantation. Most laypersons are aware of “stem cells” because of the political issues, which is a completely separate discussion. Other issues, such as xenotransplantation and oncogenesis, remain at the forefront of the clinical discussion. It is for these reasons that the model of induction neurogenesis is more appealing in terms of a plausible solution. Further work is needed to determine the exact cell intrinsic and environmental cues that drive the biological signals for de novo neurogenesis and, more importantly, how to predict pathways of migration and subsequent cellular replacement and neural network integration. As the neurobiology surrounding induction neurogenesis is uncovered, targeted thera-

pies can be directed at particular strokes. One interesting scenario would be the stereotactic injection of an entire microenvironmental milieu suspended in an artificial extracellular matrix scaffold complete with growth factors, apoptosis inhibitors, cytokines, and angiogenesis factors.

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COMMENTS

The authors provide an easy-to-follow discussion of the potential of induction neurogenesis, whereby endogenous progenitor cells are induced to replace those lost to insults such as ischemia and stroke. The discussion is worthwhile in that it presents what may be a complementary or even alternative strategy to cellular transplantation. With the goal of neurorestoration in mind, the strategy is to somehow replace the cells that have been lost, whether by cellular transplantation or induction of endogenous precursors. For these strategies to be successful, it would seem reasonable that similar appropriate modulation of extrinsic and intrinsic signals that drive precursor cell behavior must be achieved. That would mean that the source of the precursor cells, whether endogenous or exogenous, may not be as important as modulation of the signals through various means. If it turns out that the modulation of the signaling processes is best achieved in vitro, then some form of cellular transplantation would probably be necessary, even if it takes the form of the retransplantation of modified precursor cells harvested from the same patient. If the modulations can be achieved in situ and the endogenous precursor cells can be induced appropriately without having to be removed from the brain, then exogenous cellular transplantation may indeed be unnecessary.

Charles Y. Liu
Los Angeles, California

The authors present a detailed review of de novo neurogenesis in acute stroke. They begin with a discussion of central nervous system cellular transplantation, with a focus on stem cell therapy in the setting of cerebral ischemia. After a presentation of the findings to date, the authors document the potential problems encountered with neural stem cell engraftment. Next, they focus on induction neurogenesis. They begin with a brief introduction, which is followed by discussions of location, mechanism, and potential therapeutic implications.

This review of central nervous system neurogenesis after acute stroke is timely, given the relatively recent emergence of this field. The authors' comparison between exogenous stem cell replacement and de novo neurogenesis provides a good framework for the article. The conclusions derived from the discussion are poignant, encouraging further research into the mechanisms and cellular pathways involved with the processes of recruitment, migration, and integration of neural

precursors. It may be hoped that this work will entice investigators to participate in this evolving field of research.

William J. Mack
E. Sander Connolly, Jr.
New York, New York

The authors review the topic of de novo neurogenesis within the adult brain using a number of strategies, including neurotrophin delivery, gene therapy, and attempts to treat factors that might inhibit axonal regeneration. This work has been addressed adequately in other settings, but the authors have put it together for the neurosurgical readership. There is no doubt that neural restoration occurs on some level in all patients after cerebral injury or infarction. It may be related to the recovery seen in some patients. Unfortunately, much of the time, this recovery is inadequate. The authors discuss strategies to boost the patient's own ability to heal himself or herself. They argue that this may be a more effective strategy than exogenous cellular administration. It is clear that no one knows the answer to this question. Recent hypotheses related to cell delivery argue more for their role as neurotrophin "pumps" rather than as a means to reestablish segmental connections. Work is being performed on all of these fronts, and it is likely that a strategy that combines the potential benefits of several approaches will be necessary to improve neurological recovery.

Douglas Kondziolka
Pittsburgh, Pennsylvania

This review article describes the scientific frontier in an area of neural repair called induction neurogenesis—the recruitment of an endogenous neural stem cell population—with exciting possible future therapies aimed at the induction of neurogenesis as a treatment for patients who have sus-

tained acute stroke. The promise and potential of neural repair is great, especially considering the tremendous impact stroke inflicts on a population in terms of mortality and disability.

This article presents evidence of an endogenous process of neurogenesis in which all key elements for repair are present in the adult: 1) evidence of extensive progenitor migration is presented; 2) in the hippocampus, newborn neurons have been shown to establish projections in the context of neural networks; and 3) importantly, the dynamic model of neurogenesis has also been shown to be able to modulate extrinsically. However, can the progeny of adult human neural stem cells perform what we ask of them? One main issue to be taken into consideration is the fact that evolution has selected for the absence of global reconstruction in the mammalian central nervous system.

Another problem for induction neurogenesis concerns the modulation, the control of fate and migration, to which we want to subject these cells. In contrast to cell transplantation, whereby cells are primed in the perfectly controlled environment of a Petri dish, we enter into a chaotic system of a patient who has sustained a stroke. Until the above-listed issues—and more—can be overcome, neural repair by transplantation or induction neurogenesis will not be seen in clinical practice. However, let us not forget the unprecedented acceleration of scientific achievements in stem cell biology we have seen; the yielding of a long-held dogma that neurogenesis stops at birth; and the realization that by continued intensive stem cell research, no obstacles have to be considered insurmountable today.

Ulf G. Westerlund
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In-training Liaison

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Alfredo Quiñones-Hinojosa, M.D.

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