Potential of adult neural stem cells for cellular therapy

Philippe Taupin

National Neuroscience Institute, Singapore, Singapore

Abstract: Cellular therapy is the replacement of unhealthy or damaged cells or tissues by new ones. Because neurodegenerative diseases, cerebral strokes, and traumatic injuries to the central nervous system (CNS) produce neurological deficits that result from neuronal loss, cell therapy is a prominent area of investigation for the treatment of neurological diseases and injuries. Neural progenitor and stem cells generate the main phenotyes of the nervous system, and offer a model of choice for cellular therapy in the CNS. With the confirmation that neurogenesis occurs in the adult brain, and the recent isolation and characterization in vitro of neural progenitor and stem cells from the adult CNS, new strategies are being devised and have the potential to treat a broad range of CNS diseases and injuries.

Keywords: neurogenesis, central nervous system, neurodegenerative diseases, trophic factors, regeneration, transplantation

Introduction

Neural stem cells (NSCs) are selfrenewing multipotent cells that generate the main phenotype of the nervous system, neurons, astrocytes, and oligodendrocytes. Neural progenitor cells are more mature multipotent cells with limited proliferative capacity; they are generated through transient amplification of NSCs. Contrary to a long held dogma, neurogenesis occurs throughout adulthood in the mammalian brain and NSCs reside in the adult CNS (Gage 2000; Gross 2000), including human (Eriksson et al 1998; Curtis et al 2007). Neurogenesis occurs primarily in two areas of the adult mammalian brain, the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ). In the DG, newly generated neuronal cells in the subgranular zone migrate to the granular layer, where they differentiate into mature neuronal cells, and extend axonal projections to the CA3 area. In the SVZ, cells are generated in the anterior part of the SVZ, and migrate to the olfactory bulb (OB), through the rostro-migratory stream (RMS), where they differentiate into interneurons of the OB. In human, the RMS is organized, differently than in other species, around a lateral ventricular extension reaching the OB (Curtis et al 2007).

It is hypothesized that neurogenesis originate from residual stem cells in the adult brain. Self-renewing multipotent NSCs have been isolated and characterized in vitro from various areas of the adult CNS, suggesting that NSCs reside throughout the CNS and providing valuable sources of material for cellular therapy (Taupin and Gage 2002). Cell therapeutic interventions may involve both in vivo stimulation and transplantation of neural progenitor and stem cells of the adult brain.

Correspondence: Philippe Taupin
11 Jalan Tan Tock Seng,
Singapore 308433, Singapore
Tel +65 6357 7533
Fax +65 6256 9178
Email obgpjt@nus.edu.sg

Stimulation of endogenous neural progenitor and stem cells

The adult CNS is seeded with neural progenitor and stem cells. The stimulation of these cells would represent a strategy to promote regeneration in the diseased and injured

CNS. This has been particularly studied in animal models of Parkinson's disease (PD). In a recent study that report the generation of new dopaminergic neuronal cells in the adult rat substantia nigra (SN), the authors have investigated the generation of new dopaminergic neuronal cells following lesion of the SN (Zhao et al 2003). The rate of neurogenesis, as measured by BrdU labeling, was reported to be increased by 2-fold, 3 weeks following lesion induced by a systemic dose of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a model of PD. In contrast, a more recent study found no evidence of new dopaminergic neurons in the SN of 6-hydroxydopamine-lesioned hemi-Parkinsonian rodents (Frielingsdorf et al 2004). Furthermore, the generation of new dopaminergic neurons in the adult SN remains source of controversy (Lie at al 2002; Frielingsdorf et al 2004). Though the generation of new dopaminergic neuronal cells in the adult SN remains to be confirmed, hypothetically, regeneration could be promoted locally by stimulating neural progenitor and stem cells at sites of degeneration. It is the premise of cellular therapy that the environment would contribute to the development and integration of the cells in the tissue (Watt and Hogan 2000).

Investigators are aiming to identify factors promoting adult neurogenesis and the intregration of new neuronal cells after lesion. Factors like platelet-derived growth factor (PDGF-BB) and brain-derived neurotrophic factor (BDNF) induce striatal neurogenesis in adult rats with 6-hydroxydopamine lesions, with no indications of any newly born cells differentiating into dopaminergic neurons following growth factor treatment (Mohapel et al 2005). Such factors may prove to be beneficial for recovery in PD. The stimulation of endogenous neural progenitor and stem cells has also been reported in other models of CNS injuries. The implantation of dendritic cells, antigen-presenting cells of the immune system, in the spinal cord after injury in adult mice stimulates neurogenesis de novo, and locomotor recovery. Histological analysis suggests that the dendritic cells, by releasing trophic factors, may have induced regeneration of the corticospinal tract axons (Mikami et al 2004).

Alternatively, new neuronal cells are generated at sites of degeneration in the diseased brain and after CNS injuries, and originate from the SVZ. Curtis and colleagues (2003) and Tattersfield and colleagues (2004) reported an increase in SVZ neurogenesis, leading to the migration of neural progenitor cells and the formation of new neuronal cells to damaged areas of the striatum in Huntington's disease (HD) patients and in animal model of HD (quinolinic acid lesion). After experimental strokes (middle cerebral artery occlusion), new neuronal cells are detected at the major sites of degeneration, like the striatum and cortex distal to the infarction (Jiang et al 2001; Zhang et al 2001; Li et al 2002; Parent et al 2002). Cell tracking studies revealed that newly generated neuronal cells migrate partially through the RMS to the sites of degeneration, where they differentiate into the phenotypes of the degenerated nerve cells. It is estimated that 0.2% of the degenerated nerve cells in the striatum after focal ischemia are replaced (Arvidsson et al 2002; Jin et al 2003).

Hence, neurogenesis is stimulated in the adult CNS after injury, and new neuronal cells are generated at the sites of degeneration. The identification of the SVZ as the source of neural progenitor and stem cells with regenerative potential after injury suggests that strategies to promote regeneration and repair may focus on stimulating SVZ neurogenesis after injury. Both environmental enrichment and administration of various factors and molecules have been reported to promote SVZ neurogenesis. The rate of cell proliferation in the SVZ increases following exposure to an environment enriched in odors (Rochefort et al 2002). Trophic factors, like epidermal growth factor (EGF) and basic fibroblast growth factor (FGF-2) (Craig et al 1996; Kuhn et al 1997; Wagner et al 1999), and other factors, like Ginkgo biloba extract (Didier et al 2002), have also been reported to stimulate SVZ neurogenesis in rodents. Transforming growth factor-α (TGF-α) infusion into the adult rat striatum leads to migration of neuronal progenitor cells from the SVZ to the infusion site (Fallon et al 2000). These molecules and factors are potential candidates to recruit new neuronal cells from the SVZ for cellular therapy in the CNS. Future investigations will aim at identifying factors promoting neurogenesis in the degenerated areas.

The identification of the SVZ as a source of newly generated neuronal cells at the sites of degeneration after injuries presents several features that can benefit cellular therapy in the CNS. First, in the intact CNS and after injury, a significant proportion of newly generated neuronal progenitor cells in the SVZ undergo programmed cell death rather than achieving maturity, eg, 80% of the new striatal neuronal cells that are generated from the SVZ after stroke in rats die within the first weeks after the insult (Morshead et al 1992; Arvidsson et al 2001; Cameron and McKay 2001). This transient increase in newly generated neural progenitor cells provides a window of opportunity when newly generated neural progenitor cells could be salvaged, and directed to participate to the regeneration of the damaged tissue. Factors preventing cell death, like caspases (Namura et al 1998; Pompeiano et al 2000; Ekdahl et al 2001), would thus also be

potentially beneficial for cellular therapy, alone or in combination with the administration of trophic factors, and environmental enrichment that promote SVZ neurogenesis (Craig et al 1996; Kuhn et al 1997; Wagner et al 1999; Didier et al 2002; Rochefort et al 2002). Second, the identification of the SVZ, along the ventricles, as the source of neural progenitor and stem cells with regenerative potential after injury also suggests that molecules and factors could be administered either by systemic injection, intracerebroventricular, subcutaneous injection, or through the cerebrospinal fluid (CSF) to promote neurogenesis in the brain (Craig et al 1996; Kuhn et al 1997; Wagner et al 1999), but also the spinal cord (Martens et al 2002), as the central canal is a presumed location of putative NSCs (Horner et al 2000). Procedures that are less invasive would be beneficial for the treatment of the injured patients. In support to this contention, intrvavenous administration of brain-derived neurotrophic factor stimulates neurogenesis in the DG and enhances migration of subventricular zone progenitor cells to the nearby damaged striatum after ischemic stroke (Schabitz et al 2007).

Transplantation of adult-derived neural progenitor and stem cells

Neural progenitor and stem cells have been isolated and cultured in vitro from various areas of the adult CNS, including the spinal cord, and from various species (Taupin and Gage 2002), including from human biopsies and post-mortem tissues (Palmer et al 2001; Roisen et al 2001; Schwartz et al 2003), potentially allowing the generation of neural progenitor and stem cells from multiple sources for cellular therapy. Adult neural progenitor and stem cells could also be isolated from the an undamaged area of the patient's brain, expanded in vitro, and grafted back to the degenerated area(s), allowing autologous transplantation. This would obviate the need to find a matching donor and to administer drugs that suppress the immune system, like cyclosporine, to prevent tissue rejection. However, risk associated with invasive surgical procedure that would probably involves the destruction of healthy brain tissue, limits the clinical application of such strategy.

In all this shows that adult derived-NSCs represent a potent model for cellular therapy. Recent studies have confirmed the engraftment potential of adult derived neural progenitor and stem cells in animal studies (Gage et al 1995; Suhonen et al 1996; Shihabuddin et al 2000; Akiyama et al 2001; Wu et al 2001; Zhang et al 2003), confirming their potential for cellular therapy.

Cell transplantation aims mainly at delivering cells at specific sites. This is particularly suitable for the treatment of diseases, and injuries where the degeneration is limited to mainly one area, like for neurodegenerative diseases as PD and after traumatic injury to the CNS (Armstrong et al 2003; Lepore et al 2005). When the degeneration is widespread, as in neurodegenerative diseases like Alzheimer's disease, HD and multiple sclerosis, such strategy is not applicable. Neural progenitor and stem cells migrate to tumor (Aboody et al 2000; Brown et al 2003; Glass et al 2005), injured (Macklis et al 1993; Veizovic et al 2001; Modo et al 2004; Boockvar et al 2005), diseased sites (Pluchino et al 2003), when transplanted in the CNS, or administered either by systemic injection, or through the cerebrospinal fluid (CSF) by injecting cells into the 4th ventricle in the rat. The injected cells conveyed to the damaged areas, where they integrate the host tissue. A recent study has reported that the systemic injection of neural progenitors and stem cells may provide significant clinical benefits in an animal model of multiple sclerosis (Pluchino et al 2003). Thus, NSC therapy may provide a therapeutic tool for the treatment of a broad range of neurological diseases and injuries. Such migratory properties of NSCs can be used as a general mode for administering neural progenitor and stem cells for cellular therapy, avoiding surgical procedures, and their associated risks and secondary effects. Hence, systemic injection and injection through CSF are regarded as promising ways to administer NSCs for cellular therapy, particularly for the treatment of spinal cord injuries (Wu et al 2002; Fujiwara et al 2004).

Adult neural progenitor and stem cells can be genetically modified by retroviral-mediated infection, rendering them a vehicle for gene therapy. Mouse and human neural progenitor and stem cells genetically modified to express acid sphingomyelinase reverse lysosomal storage pathology when transplanted into animal models of Niemann-Pick's disease (Shihabuddin et al 2004; Sidman et al 2007). This highlights the potential of genetically modified NSCs for the treatment of lysosomal storage diseases and other genetic diseases of the CNS. The potential of genetically modified NSCs is further highlighted by their potential for the treatment of brain tumors. Grafted neural progenitor and stem cells migrate to tumors. The properties of NSCs to be genetically modified and to migrate to tumor sites have been proposed for the treatment of brain tumors. It is proposed to genetically modified NSCs with "suicide genes", like genes coding for cytolytic activities or anti-tumor cytokines, to attack and destroy brain tumor cells. Intravascular administration of neural progenitor and stem cells genetically engineered to express interferon-b lead to tumor regression in mice (Kim et al 2006; Dickson et al 2007). This strategy further extends the use of cell engineering of NSCs for cancer therapy in the CNS.

Altogether these data show that cell transplantation of adult NSCs provide a model of choice for cellular therapy in the CNS, and has the potential to treat a broad range of CNS diseases and injuries, ranging from neurodegenerative diseases, strokes, spinal cord injuries, genetic diseases of the CNS, to brain tumors.

In a study where human fetal neural progenitor and stem cells were injected after spinal cord injury in mice, the improvements in walking disappeared following treatment with diphtheria toxin, which kills only human cells and not mouse cells (Cummings et al 2005). This suggests that the grafted neural progenitor and stem cells themselves are responsible for recovery. Beside the replacement of the degenerated cells by the grafted cells, grafted NSCs may also promote functional recovery by promoting the survival of injured neuronal cells through the secretion of neurotrophic factors (Ourednik et al 2002; Lu et al 2003; Llado et al 2004; Pfeifer et al 2004; Yan et al 2004), and its interaction with the injured brain and immune system (Park et al 2002; Pluchino et al 2005), further underlining the relevance of NSCs for cellular therapy in the CNS.

Conclusion

Because of their potential to generate the different cell types of the CNS, NSCs represent a model of choice for cellular therapy in the CNS. The recent confirmation that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS opens new opportunities for cellular therapy. On the one hand, new neuronal cells are generated at the sites of degeneration in the diseased and injured brain. Though the CNS has limited capacity to recover after injury, the data shows that the CNS has the ability to repair itself after injury. On the other hand, the grafting of adult neural progenitor and stem cells offers an alternative for cellular therapy in the CNS. Hence, adult NSCs offer a potent and promising model for cellular therapy. Futures studies will aim at identifying the factors and mechanisms underlying adult neurogenesis, to promote and enhance the regenerative potential of endogenous NSCs. Isolated adult neural progenitor and stem cell populations are heterogeneous, likely a factor limiting their potential for recovery. Future studies will aim at identifying the NSCs, enriched them, as a source of homogeneous populations of NSCs for cellular therapy. Futures directions will aim at addressing the challenges and limitations of adult NSC therapy. Particularly, to what extent newly formed or transplanted neural progenitor and stem cells integrate and become functional? What are the potential and risk that newly formed or transplanted neural progenitor and stem cells establish the wrong connections or transplanted neural progenitor and stem cells develop into tumors upon grafting? These questions will need to be answered before the adult NSCs could be brought to therapy.

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References

Aboody KS, Brown A, Rainov NG, et al. 2000. Neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas. *Proc Natl Acad Sci USA*, 97:12846–51. Erratum in: 2001. *Proc Natl Acad Sci USA*, 98:777.

Akiyama Y, Honmou O, Kato T, et al. 2001. Transplantation of clonal neural precursor cells derived from adult human brain establishes functional peripheral myelin in the rat spinal cord. *Exp Neurol*, 167:27–39.

Armstrong RJ, Tyers P, Jain M, et al. 2003. Transplantation of expanded neural precursor cells from the developing pig ventral mesencephalon in a rat model of Parkinson's disease. *Exp Brain Res*, 151:204–17.

Arvidsson A, Kokaia Z, Lindvall O. 2001. N-methyl-D-aspartate receptor-mediated increase of neurogenesis in adult rat dentate gyrus following stroke. *Eur J Neurosci*, 14:10–18.

Arvidsson A, Collin T, Kirik D, et al. 2002. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat Med*, 8:963–70.

Boockvar JA, Schouten J, Royo N, et al. 2005. Experimental traumatic brain injury modulates the survival, migration, and terminal phenotype of transplanted epidermal growth factor receptor-activated neural stem cells. *Neurosurgery*, 56:163–71.

Brown AB, Yang W, Schmidt NO, et al. 2003. Intravascular delivery of neural stem cell lines to target intracranial and extracranial tumors of neural and non-neural origin. *Hum Gene Ther*, 14:1777–85.

Cameron HA, McKay RD. 2001. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. *J Comp Neurol*, 435:406–17.

Craig CG, Tropepe V, Morshead CM, et al. 1996. In vivo growth factor expansion of endogenous subependymal neural precursor cell populations in the adult mouse brain. *J Neurosci*, 16:2649–58.

Cummings BJ, Uchida N, Tamaki SJ, et al. 2005. Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice. *Proc Natl Acad Sci USA*, 102:14069–74.

Curtis MA, Penney EB, Pearson AG, et al. 2003. Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. *Proc Natl Acad Sci USA*, 100:9023–7.

Curtis MA, Kam M, Nannmark U, et al. 2007. Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. *Science*, 315:1243–9.

Dickson PV, Hamner JB, Burger RA, et al. 2007. Intravascular administration of tumor tropic neural progenitor cells permits targeted delivery of interferon-beta and restricts tumor growth in a murine model of disseminated neuroblastoma. *J Pediatr Surg*, 42:48–53.

Didier A, Jourdan F. 2002. The Ginkgo biloba extract modulates the balance between proliferation and differentiation in the olfactory epithelium of adult mice following bulbectomy. *Cell Mol Biol*, 48:717–23.

Ekdahl CT, Mohapel P, Elmer E, et al. 2001. Caspase inhibitors increase short-term survival of progenitor-cell progeny in the adult rat dentate gyrus following status epilepticus. *Eur J Neurosci*, 14:937–45.

Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. 1998. Neurogenesis in the adult human hippocampus. *Nat Med*, 4:1313–7.

Fallon J, Reid S, Kinyamu R, et al. 2000. In vivo induction of massive proliferation, directed migration, and differentiation of neural cells in the adult mammalian brain. *Proc Natl Acad Sci USA*, 97:14686–91. Erratum in: 2001. *Proc Natl Acad Sci USA*, 98:8157.

Frielingsdorf H, Schwarz K, Brundin P, et al. 2004. No evidence for new dopaminergic neurons in the adult mammalian substantia nigra. *Proc Natl Acad Sci USA*, 101:10177–82.

Fujiwara Y, Tanaka N, Ishida O, et al. 2004. Intravenously injected neural progenitor cells of transgenic rats can migrate to the injured spinal cord and differentiate into neurons, astrocytes and oligodendrocytes. *Neurosci Lett*, 366:287–91.

Gage FH, Coates PW, Palmer TD, et al. 1995. Survival and differentiation of adult neuronal progenitor cells transplanted to the adult brain. *Proc Natl Acad Sci USA*, 92:11879–83.

Gage FH. 2000. Mammalian neural stem cells. *Science*, 287:1433–8.

Gross CG. 2000. Neurogenesis in the adult brain: death of a dogma. *Nat Rev Neurosci*, 1:67–73.

Horner PJ, Power AE, Kempermann G, et al. 2000. Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. *J Neurosci*, 20:18–2228.

Jiang W, Gu W, Brannstrom T, et al. 2001. Cortical neurogenesis in adult rats after transient middle cerebral artery occlusion. *Stroke*, 32:1201–7.

Jin K, Sun Y, Xie L, et al. 2003. Directed migration of neuronal precursors into the ischemic cerebral cortex and striatum. *Mol Cell Neurosci*, 24:171–89.

Glass R, Synowitz M, Kronenberg G, et al. 2005. Glioblastoma-induced attraction of endogenous neural precursor cells is associated with improved survival. *J Neurosci*, 25:2637–46.

Kim SK, Kim SU, Park IH, et al. 2006. Human neural stem cells target experimental intracranial medulloblastoma and deliver a therapeutic gene leading to tumor regression. *Clin Cancer Res*, 12:5550–6.

Kuhn HG, Winkler J, Kempermann G, et al. 1997. Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. *J Neurosci*, 17:5820–9.

Lepore AC, Bakshi A, Swanger SA, et al. 2005. Neural precursor cells can be delivered into the injured cervical spinal cord by intrathecal injection at the lumbar cord. *Brain Res*, 1045:206–16.

Li Y, Chen J, Chopp M. 2002. Cell proliferation and differentiation from ependymal, subependymal and choroid plexus cells in response to stroke in rats. *J Neurol Sci*, 193:137–46.

Lie DC, Dziewczapolski G, Willhoite AR, et al. 2002. The adult substantia nigra contains progenitor cells with neurogenic potential. *J Neurosci*, 22:6639–49.

Llado J, Haenggeli C, Maragakis NJ, et al. 2004. Neural stem cells protect against glutamate-induced excitotoxicity and promote survival of injured motor neurons through the secretion of neurotrophic factors. *Mol Cell Neurosci*, 27:322–31.

Lu P, Jones LL, Snyder EY, et al. 2003. Neural stem cells constitutively secrete neurotrophic factors and promote extensive host axonal growth after spinal cord injury. *Exp Neurol*, 181:115–29.

Macklis JD. 1993. Transplanted neocortical neurons migrate selectively into regions of neuronal degeneration produced by chromophore-targeted laser photolysis. *J Neurosci*, 13:3848–63.

Martens DJ, Seaberg RM, van der Kooy D. 2002. In vivo infusions of exogenous growth factors into the fourth ventricle of the adult mouse brain increase the proliferation of neural progenitors around the fourth ventricle and the central canal of the spinal cord. *Eur J Neurosci*, 16:1045–57.

Mikami Y, Okano H, Sakaguchi M, et al. 2004. Implantation of dendritic cells in injured adult spinal cord results in activation of endogenous neural stem/progenitor cells leading to de novo neurogenesis and functional recovery. *J Neurosci Res*, 76, 453–65.

Modo M, Mellodew K, Cash D, et al. 2004. Mapping transplanted stem cell migration after a stroke: a serial, in vivo magnetic resonance imaging study. *Neuroimage*, 21:311–17.

Mohapel P, Frielingsdorf H, Haggblad J, et al. 2005. Platelet-Derived Growth Factor (PDGF-BB) and Brain-Derived Neurotrophic Factor (BDNF) induce striatal neurogenesis in adult rats with 6-hydroxydopamine lesions. *Neurosci*, 132, 767–76.

Morshead CM, van der Kooy D. 1992. Postmitotic death is the fate of constitutively proliferating cells in the subependymal layer of the adult mouse brain. *J Neurosci*, 12:249–56.

Namura S, Zhu J, Fink K, et al. 1998. Activation and cleavage of caspase-3 in apoptosis induced by experimental cerebral ischemia. *J Neurosci*, 18:3659–8.

Ourednik J, Ourednik V, Lynch WP, et al. 2002. Neural stem cells display an inherent mechanism for rescuing dysfunctional neurons. *Nat Biotechnol*, 20:1103–10.

Palmer TD, Schwartz PH, Taupin P, et al. 2001. Cell culture. Progenitor cells from human brain after death. *Nature*, 411:42–3.

Parent JM, Vexler ZS, Gong C, et al. 2002. Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. *Ann Neurol*, 52:802–13.

Park KI, Teng YD, Snyder EY. 2002. The injured brain interacts reciprocally with neural stem cells supported by scaffolds to reconstitute lost tissue. *Nat Biotechnol*, 20:1111–17.

Pfeifer K, Vroemen M, Blesch A, et al. 2004. Adult neural progenitor cells provide a permissive guiding substrate for corticospinal axon growth following spinal cord injury. *Eur J Neurosci*, 20:1695–1704.

Pluchino S, Quattrini A, Brambilla E, et al. 2003. Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. *Nature*, 422:688–94.

Pluchino S, Zanotti L, Rossi B, et al. 2005. Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature*, 436:266–71.

Pompeiano M, Blaschke AJ, Flavell RA, et al. 2000. Decreased apoptosis in proliferative and postmitotic regions of the Caspase 3-deficient embryonic central nervous system. *J Comp Neurol*, 423:1–12.

Rochefort C, Gheusi G, Vincent JD, et al. 2002. Enriched odor exposure increases the number of newborn neurons in the adult olfactory bulb and improves odor memory. *J Neurosci*, 22:2679–89.

Roisen FJ, Klueber KM, Lu CL, et al. 2001. Adult human olfactory stem cells. *Brain Res*, 890:11–22.

Schabitz WR, Steigleder T, Cooper-Kuhn CM, et al. 2007. Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis. *Stroke*, in press.

Schwartz PH, Bryant PJ, Fuja TJ, et al. 2003. Isolation and characterization of neural progenitor cells from post-mortem human cortex. *J Neurosci Res*, 74:838–51.

Shihabuddin LS, Horner PJ, Ray J, et al. 2000. Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus. *J Neurosci*, 20:8727–35.

Shihabuddin LS, Numan S, Huff MR, et al. 2004. Intracerebral transplantation of adult mouse neural progenitor cells into the Niemann-Pick-A mouse leads to a marked decrease in lysosomal storage pathology. *J Neurosci*, 24:10642–51.

Sidman RL, Li J, Stewart GR, et al. 2007. Injection of mouse and human neural stem cells into neonatal Niemann-Pick A model mice. *Brain Res*, 1140:195–204.

Suhonen JO, Peterson DA, Ray J, et al. 1996. Differentiation of adult hippocampus-derived progenitors into olfactory neurons in vivo. *Nature*, 383:624–7.

Tattersfield AS, Croon RJ, Liu YW, et al. 2004. Neurogenesis in the striatum of the quinolinic acid lesion model of Huntington's disease. *Neurosci*, 127:319–32.

Taupin P, Gage FH. 2002. Adult neurogenesis and neural stem cells of the central nervous system in mammals. *J Neurosci Res*, 69:745–9.

Veizovic T, Beech JS, Stroemer RP, et al. 2001. Resolution of stroke deficits following contralateral grafts of conditionally immortal neuroepithelial stem cells. *Stroke*, 32:1012–19.

Wagner JP, Black IB, DiCicco-Bloom E. 1999. Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor. *J Neurosci,* 19:6006–16.

Watt FM, Hogan BL. 2000. Out of Eden, stem cells and their niches. *Science*, 287:1427–30.

Wu S, Suzuki Y, Kitada M, et al. 2001. Migration, integration, and differentiation of hippocampus-derived neurosphere cells after transplantation into injured rat spinal cord. *Neurosci Lett*, 312:173–6.

Wu S, Suzuki Y, Kitada M, et al. 2002. New method for transplantation of neurosphere cells into injured spinal cord through cerebrospinal fluid in rat. *Neurosci Lett*, 318:81–4.

Yan J, Welsh AM, Bora SH, et al. 2004. Differentiation and tropic/trophic effects of exogenous neural precursors in the adult spinal cord. *J Comp Neurol*, 480:101–14.

Zhang RL, Zhang ZG, Zhang L, et al. 2001. Proliferation and differentiation of progenitor cells in the cortex and the subventricular zone in the adult rat after focal cerebral ischemia. *Neurosci*, 105:33–41.

Zhang RL, Zhang L, Zhang ZG, et al. 2003. Migration and differentiation of adult rat subventricular zone progenitor cells transplanted into the adult rat striatum. *Neurosci*, 116:373–82.

Zhao M, Momma S, Delfani K, et al. 2003. Evidence for neurogenesis in the adult mammalian substantia nigra. *Proc Natl Acad Sci USA*, 100:7925–30.