

Disease Targets and Strategies for the Therapeutic Modulation of Endogenous Neural Stem and Progenitor Cells

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Neural stem cells, able to self-renew and give rise to both neurons and glia, line the cerebral ventricles of the adult human brain. Humans also harbor lineage-restricted neuronal progenitors in the hippocampus and glial progenitor cells in both the gray and white matter of the forebrain. These various stem and progenitor cell types may provide targets for pharmacotherapy for a variety of disorders of the central nervous system. Each resident progenitor phenotype may be mobilized and induced to differentiate *in vivo* by the actions of both exogenous growth factors and small molecule modulators of progenitor-selective signaling pathways. This strategy may be particularly efficacious in neurodegenerations such as Huntington's disease, in which lost neurons may be replenished through the directed induction of progenitor cells lining the ventricular wall of the affected striatum. Similarly, the mobilization of glial progenitor cells may permit the introduction of new oligodendrocytes to demyelinated regions of adult white matter. Our rapidly increasing understanding of the molecular control of progenitor cell mobilization and differentiation should provide a wealth of new opportunities for recruiting endogenous progenitors as a means of treating neurological disease.

NEURAL STEM AND PROGENITOR CELLS OF THE HUMAN BRAIN

The developing brain arises from a layer of neuroepithelial stem cells that surrounds the lumen of the early neural tube. As ontogeny proceeds, this lumen becomes segregated into the ventricles of the developing brain, the layer surrounding which develops as the ventricular zone (VZ). Long after the cessation of brain development, multipotential neural stem cells continue to line the cerebral ventricles of the forebrain in the subependymal layer, an adult vestige of the VZ^{1,2} (for

review see refs. 3–5). In addition, their daughter cells, which include lineage-restricted neuronal progenitors, remain within the ventricular subependyma throughout its rostral extensions to the olfactory bulb.^{6–13} These neuronally restricted progenitor cells may be considered “transit amplifying cells,” the phenotypically biased, still-mitotic progeny of uncommitted stem cells.^{14,15} Along with an analogous population of neuronal progenitor cells in the subgranular zone (SGZ) of the dentate gyrus,¹⁶ which contributes new neurons to the hippocampus, the subependymal progenitors of the lateral ventricular wall appear to comprise the major transit amplifying pools of neurogenic progenitors in the vertebrate brain^{17,18} (Figure 1). Importantly, each of these populations has been identified in, mapped, and isolated from the adult human brain, as in experimental animals.^{8,19–22}

Besides these populations of neuronal progenitors, glial progenitor cells are also abundant in the adult brain. In humans, these cells are dispersed throughout the subcortical white matter,^{23–25} as in other infraprimate mammals.²⁶ Adult glial progenitor cells retain multilineage competence,^{25,27} and can become robustly neurogenic under appropriate conditions.²⁸ In the adult human, significant pools of glial progenitor cells have now been identified in both the cortex²⁹ and subcortical white matter.^{25,28} Indeed, glial progenitor cells appear to comprise by far the most abundant progenitor phenotype of the adult human brain, comprising as much as 4% of all cells in the mature white matter.^{23,25,28,30} They comprise an abundant reservoir of widely dispersed, cycling, multipotential progenitors, which though restricted to glial phenotype *in vivo*, are multipotential and neurogenic when removed from the fate-restrictive environment of the adult parenchyma.²⁹ Although the incidence of analogous progenitor cells in the gray matter of adult humans has not yet been evaluated, these cells are abundant in rodents,²⁷ and there is no reason to think that they are any less so in

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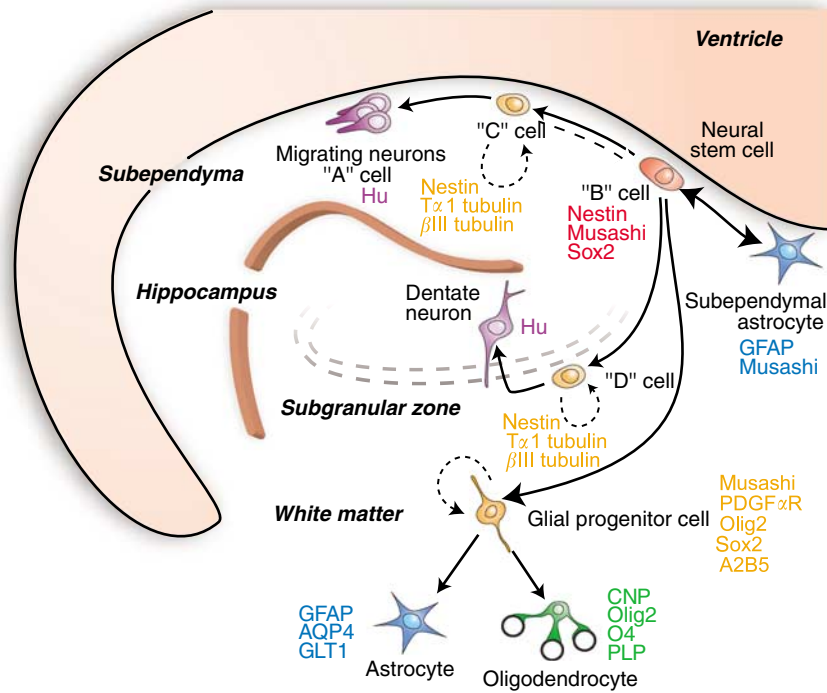


Figure 1 Stem and progenitor cells of the adult human brain. This schematic illustrates the basic categories of progenitor cells in the adult brain and their lineal relationships, as well as markers and combinations thereof that permit their enrichment. The human temporal lobe is schematized here; it includes periventricular neural stem cells (red) that generate at least three populations of potentially neurogenic transit amplifying progenitors of both neuronal and glial lineages (yellow). These include the neuronal progenitor cells of the ventricular subependyma, those of the SGZ of the dentate gyrus, and the glial progenitor cells of the subcortical white matter. Each transit amplifying pool may then give rise to differentiated progeny appropriate to their locations, including neurons (purple), oligodendrocytes (green), and parenchymal astrocytes (blue). A-D cell stage terminology derived from refs. 5, 98. Markers defining each stage have been reviewed previously in ref. 99. Figure adapted from ref. 17.

humans. Importantly, like the lineage-restricted progenitors of the ventricular subependyma and hippocampus, the adult glial progenitor cell may also be considered transit-amplifying; it is able to divide and yield variably restricted daughters that are themselves still mitotic but incapable of sustained self-renewal.²⁹

Together, these different classes of progenitors constitute the major known categories of neural precursor cells in the adult human central nervous system (reviewed in ref. 17). Their pharmacotherapeutic significance lies in the inherent potential of each to be targeted for mobilization and directed differentiation to therapeutically required phenotypes. As such, adult progenitor cells may lie at the intersection of cell-, gene-, and small molecule-based treatment strategies.

ENDOGENOUS PROGENITOR CELLS ARE MOBILIZED BY INJURY AND DISEASE

Over the past several years, a number of studies of both compensatory neurogenesis after injury and induced neurogenesis in the setting of neurodegeneration have highlighted the potential of mobilizing endogenous progenitor cells for repair purposes. In particular, the persistence in abundance of both neural stem cells and their neuronal progeny in the striatal wall of the lateral ventricle suggested the potential utility of these cells in restoring lost striatal neuronal

populations. Compensatory replacement of striatal neurons from resident progenitors was identified in experimental stroke models by several groups, who described neuronal recruitment into the neostriatum after focal ischemic injury.^{31–34} Similarly, Nakafuku and coworkers³⁵ described compensatory replacement of hippocampal pyramidal neurons, another periventricular subcortical neuronal pool, although the latter observation remains to be replicated. Other groups have reported recently apparent compensatory neurogenesis in the striatum of Huntington’s disease patients³⁶ and in the dentate gyrus of the hippocampus of Alzheimer’s patients.³⁷ Together, these instances of compensatory neurogenesis suggest the potential for recruiting new neurons from resident progenitor cells as a means of treating degenerative conditions of each of these subcortical structures (Figure 2).

ENDOGENOUS PROGENITOR CELLS CAN BE EXOGENOUSLY MOBILIZED

A number of humoral growth factors have been identified as modulating the mitotic expansion and differentiated fate of neural stem cells. Epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2), each of which have mitogenic effects on neuronal progenitor cells of the adult subependyma, can both potentiate neuronal replacement in

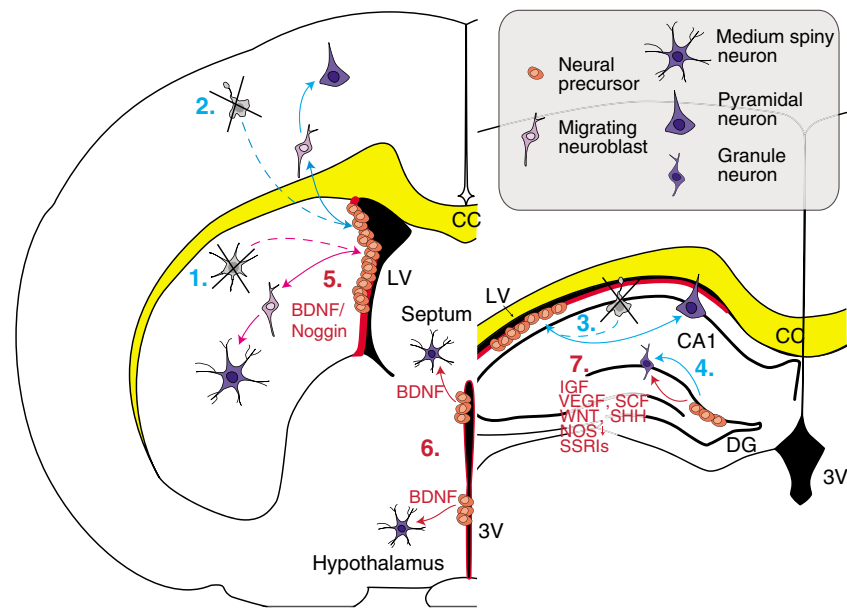


Figure 2 Loci for modulating neuronal recruitment to the adult brain. This schematic illustrates both the described loci of compensatory (1–4) and experimenter-induced (5–7) neurogenesis in the adult rat brain, focusing on the neostriatum and cortex and hippocampus. Relevant references as noted. *Loci of experimental compensatory neurogenesis* include the neostriatum (1), cortex (2), and hippocampal pyramidal (3) and dentate (4) layers following either stroke or more discrete intralaminar neuronal ablation.¹⁰⁰ In patients, compensatory neurogenesis has similarly been reported, in response to neurodegeneration in both Huntington's disease³⁶ and Alzheimer's disease,³⁷ in the striatum and dentate gyrus, respectively. *Loci of induced neurogenesis* include the neostriatum (5) and diencephalon (6) in response to BDNF, with potentiation of the striatal response with concurrent BMP suppression via noggin. Neuronal production may also be induced in the dentate gyrus of the hippocampus (7), in response to a variety of neurotrophic and mitogenic agents, as well as to NOS inhibition and serotonergic agonists. Figure adapted from ref. 81.

the presence of permissive signals for neuronal differentiation. Yet these agents appear to act solely as mitogens when used alone. EGF delivery to the adult ventricular subependyma leads largely to gliogenesis,³⁸ and FGF2 infusion increases neuronal recruitment to the olfactory bulb but nowhere else; neurons generated under the sole influence of FGF2 do not depart from their typical migratory paths to enter any other subcortical structures along their migratory route.³⁹ A number of other ligands for receptor tyrosine kinases have been found to drive mitotic expansion by neural stem and progenitor cells, including vascular endothelial growth factor (VEGF) and stem cell factor, through the VEGF-receptor 2 and c-kit receptors, respectively.^{40,41} Similarly, inhibition of nitric oxide, which appears to tonically suppress progenitor turnover in the adult central nervous system, has also been associated with increased neuronal production in the olfactory subependyma, bulb, and dentate gyrus.⁴² However, none of these different agents have been shown to view heterotopic neuronal addition *in vivo*, *i.e.*, the recruitment of new neurons into otherwise non-neurogenic regions of the adult brain.

To achieve the addition of new neurons to the mature brain, several groups have instead focused on delivering the trkB ligand brain-derived neurotrophic factor (BDNF) to the adult progenitor pool. BDNF had previously been shown to stimulate the production and survival of new neurons from adult precursor cells *in vitro*.^{9,43–45} On this basis, Benraiss

et al. used adenoviral gene therapy to deliver the gene encoding BDNF to the brains of adult rats. They noted that a single, one-time injection of an adenovirus expressing BDNF into the forebrain ventricles of adult rats induced the production of new neurons from neural progenitor cells in the ventricular lining, the subependyma.⁴⁶ Most of the new neurons migrated to the olfactory bulb, again a normal site of neuronal addition in the rodent brain. However a large number of new neurons also invaded the neostriatum, a region of the brain that does not typically produce or accept new neurons in the normal, uninjured brain. Of note, similar results were obtained using BDNF protein infusion, which yielded evidence of diencephalic and striatal neuronal addition.⁴⁷ In the striatum, these newly generated neurons stably integrated largely as one specific cell type, the medium spiny neuron.^{46,48} Importantly, these are the cells that are typically lost in Huntington's disease, suggesting that adenoviral BDNF (AdBDNF)-induced cells may be able to replace directly the very phenotype lost in the course of Huntington's disease.

INDUCED NEUROGENESIS FOR THE TREATMENT OF HUNTINGTON'S DISEASE

In vivo, most neural stem cells divide either to die or differentiate as glia, unless otherwise challenged.⁴⁹ On this basis, and in light of BDNF's efficacy in inciting medium spiny neuronal recruitment to the adult neostriatum,

Chmielnicki *et al.* asked whether this process might be enhanced by the concurrent suppression of glial differentiation. As gliogenesis by neural stem cells appears to be mediated by the proglial bone morphogenetic proteins,^{50,51} Chmielnicki⁵² used periventricular overexpression of noggin, a developmental inhibitor of the bone morphogenetic proteins, to suppress glial production by subependymal progenitors. In doing so, they capitalized on observations that noggin is selectively expressed in regions of ongoing neurogenesis *in vivo*, suggesting that its periventricular overexpression might both extend the geographic range of subependymal neurogenesis, and potentiate its quantitative extent. This proved to be the case: AdNoggin co-injected with AdBDNF strongly accentuated striatal neurogenesis, such that treated rats exhibited >350 new neurons per mm³ within a month after viral injection, threefold more than rats injected with AdBDNF alone.^{48,53} These data indicated that noggin acts to suppress gliogenesis by adult subependymal progenitors, and can thereby potentiate the BDNF-induced recruitment of new medium spiny neurons from periventricular neural stem cells.

To assess the feasibility of this strategy for treating neurodegenerative diseases, Cho *et al.* studied the effect of concurrent AdBDNF and AdNoggin injection in R6/2 mice, a mutant transgenic for a approximately 150 polyglutamine repeat in the huntingtin gene. These mice display a progressive behavioral phenotype associated with neuronal degeneration in the neostriatum.⁵⁴ Cho *et al.* asked if AdBDNF and AdNoggin could stimulate neuronal recruitment from VZ progenitor cells into the neostriata of R6/2 mice. They found that R6/2 huntingtin-mutant mice treated with AdBDNF and AdNoggin indeed exhibited substantial striatal neuronal addition, with the recruitment of new medium spiny neurons, throughout the medial neostriatum.^{55,56} Thus, the overexpression of BDNF and noggin in the adult huntingtin-mutant forebrain VZ seems sufficient to induce the addition of new neurons to the diseased neostriatum. Since these newly induced medium spiny neurons can extend fibers to their normal efferent targets in the globus pallidus, their induction in the huntingtin-mutant brain may permit the functional replacement of those neurons lost to disease. Indeed, as BDNF may be used to stimulate human subependymal precursor cells as well as those of rodents,^{21,57} we can predict that the ventricular overexpression of BDNF might serve to induce new medium spiny neurons in both humans and in experimental animals. If so, then the induction of striatal neuronal recruitment from endogenous progenitor cells might prove a viable therapeutic modality for Huntington's disease, as well as for such other causes of striatal neuronal loss as striatonigral degeneration and stroke (**Figure 2**).

Importantly, these studies highlighted the potential value of glial suppression as an end in itself. Specifically, these experiments established the value of inhibiting glial, differentiation while mobilizing native progenitors, for the purpose of adding new neurons to the adult forebrain.

Similarly the successful use of noggin to suppress subependymal gliogenesis also suggests the bone morphogenetic protein pathway as a valuable target for efforts to suppress central nervous system astrocytosis and glial scar formation more broadly, such a strategy might prove important in disorders as diverse as spinal cord injury and post-stroke epilepsies, in which the delimitation and moderation of reactive astrocytosis may have profound therapeutic benefit.

PROGENITOR MOBILIZATION FOR THE HIPPOCAMPAL ATROPHIES

The adult hippocampus exhibits persistent neurogenesis throughout life in animals, and appears to do so in humans as well.^{19,22,58} These new hippocampal neurons may be required for the acquisition of new memories (reviewed in ref. 59), and the modulation of adult hippocampal neurogenesis has been associated with both learning and affective states (the latter reviewed in ref. 60). Indeed, the diminution of dentate neurogenesis has been linked to both memory disorders and depression, whereas antidepressants have been associated with increased dentate neurogenesis.^{61,62} As such, clinical syndromes such as the pseudodementia of depression may prove to be specifically associated with deficits in dentate neurogenesis. The potential modulation of hippocampal neurogenesis has therefore become of great interest to neurologists and psychiatrists alike.

New neurons are added to the adult dentate gyrus from progenitors in the subgranular zone (SGZ) of the hippocampus, a layer which is developmentally contiguous with the most posterior reaches of the subependymal zone of the lateral ventricle.^{63,64} SGZ progenitors respond to FGF2, insulin-like growth factor 1, and VEGF with mitotic expansion,^{40,65,66} the efficacy of which may increase in the setting of antecedent factor depletion or injury. VEGF in particular has elicited much recent interest, in that it may act upon neural progenitors and vascular endothelial cells in tandem.⁶⁷⁻⁶⁹ In this regard, adeno-associated viral overexpression of vascular endothelial growth factor, in the adult hippocampus, has been associated with both enhanced dentate neurogenesis and improved cognitive performance.⁷⁰ In addition to these receptor tyrosine kinase-targeted growth factors, both the sonic hedgehog and the wnt proteins, morphogens more often implicated in phenotypic induction and regionalization of the developing nervous system, may also regulate the proliferation of adult neural progenitor cells.⁷¹⁻⁷³ Besides the peptide growth factors, other positive regulators of hippocampal neurogenesis include environmental enrichment, exercise, gonadal and adrenal steroids, and serotonin agonists, all of which have been associated with mood elevation and improved performance in a variety of memory-dependent tasks.^{61,74-79} The very malleability of hippocampal neurogenesis argues that it may prove an especially amenable target for pharmacotherapy. The modulation of SGZ neurogenesis may thereby prove beneficial not only in the affective disorders, but also as adjunctive therapy in the degenerative dementias associated with hippocampal atrophy.

PROGENITOR INDUCTION IN PARKINSON'S DISEASE

Parkinson's disease is due in large part to the loss of the neurons of the substantia nigra pars compacta, a dopaminergic projection nucleus lying in the ventral midbrain, which extends its fibers to the caudate-putamen, to which it provides dopaminergic input. Numerous studies, using both tissue-derived and embryonic stem cell-derived dopaminergic neurons, have attempted to treat Parkinson's disease using cell grafts delivered to the caudate-putamen (for reviews see refs. 80, 81). Although promising results have been reported by a number of groups using different preclinical models,⁸² the clinical safety and utility of dopaminergic cell grafts, regardless of their source, remains to be demonstrated.

Alternatively, the neurons lost to Parkinson's disease might optimally be regenerated from a patient's own store of endogenous progenitors, rather than delivered as an allograft. Yet Parkinson's disease arises from the loss of dopaminergic neurons of the substantia nigra, which lies in the midbrain, distant from the luminal walls of the cerebral aqueduct or ventricular system. In such parenchymal regions lacking contiguity to a source of VZ progenitors, it remains unclear whether an inductive approach to regeneration is feasible in adults. To be sure, the mesencephalic VZ continues to harbor neural stem cells, and these are especially biased toward dopaminergic neurogenesis.⁸³ However, whether these cells are available to, or ever recruited by, the adult substantia nigra is unclear. Several groups have instead attempted to induce dopaminergic neurogenesis from parenchymal progenitors residing within the substantia nigra itself.⁸⁴ Yet although these nigral progenitors could be readily stimulated to generate neurons *in vitro*, these cells were not dopaminergic. Indeed, even if dopaminergic neurogenesis from these cells might be accomplished *in vitro*, whether nigral progenitor-derived dopaminergic neurons could be induced *in vivo*, and then directed to extend axons specifically to the distant neostriatum, remains problematic. The induction of dopaminergic neurogenesis from resident progenitors in the substantia nigra thus remains a formidable challenge.

To circumvent our current ignorance of how to effect long-distance axonal extension from the nigra to the caudate-putamen, investigators have attempted to generate dopaminergic neurons from striatal progenitors, thereby recruiting new dopaminergic neurons directly to the caudate-putamen. In particular, introduction of transforming growth factor- α , an epidermal growth factor receptor ligand, to the adult lateral ventricle after catecholaminergic cell injury was found to be sufficient to induce the recruitment of new dopaminergic neurons to the striatum.⁸⁵ Yet although dopaminergic, these were not nigral neurons, but more likely heterotopically recruited olfactory dopaminergic neurons; their ability to be recruited in the numbers and distribution required for the amelioration of Parkinson's disease remains unclear.

MOBILIZATION OF ENDOGENOUS GLIAL PROGENITOR CELLS AS A REMYELINATION STRATEGY

Glial progenitor cells are obvious choices as vectors for cell-based therapy of diseases of myelin, in that they are competent to differentiate as oligodendrocytes after transplantation.^{30,86–88} Accordingly, glial progenitors and less-restricted neural stem cells have been tested extensively in models of acquired adult demyelination, including both experimental allergic encephalomyelitis and spinal cord injury. However, their more immediate value may be in mediating the myelination of congenitally dysmyelinated hosts^{86,89} and in rectifying enzymatic deficiencies by distributing themselves throughout the deficient host neuraxis after perinatal allograft.^{90,91}

Yet, besides these transplantation-directed strategies for glial progenitor cell-based therapy, a number of disease targets may benefit from the mobilization and directed induction of desired glial phenotypes from endogenous glial progenitor cells. Indeed, the sheer abundance of these cells in the adult human brain—more than 3% of all white matter cells can be isolated as nominal oligodendrocyte progenitor cells²⁵—points to an accessible reservoir of cells potentially amenable to both genetic and pharmacological induction. Sim *et al.*⁹² have capitalized upon the ubiquity and lineage potential of these cells by isolating them from the adult human brain and then assessing their differentially expressed genes, relative to the white matter from which each isolate was derived. By this means, signaling pathways differentially active in adult human glial progenitor cells were identified and their interactions assessed. Using this approach, Sim *et al.* highlighted the relative importance of receptor tyrosine phosphatase- β/ζ in the maintenance of adult glial progenitor cells. They noted that the suppression of receptor tyrosine phosphatase- β/ζ activity, using either an oxovanadate inhibitor of receptor tyrosine phosphatase- β/ζ , or lentiviral RNAi-based receptor tyrosine phosphatase- β/ζ knockdown, resulted in the induced differentiation of adult glial progenitors as oligodendrocytes. This work thereby identified both a class of compounds and its molecular target, by which an endogenous progenitor cell might be modulated to produce a desired phenotype of potential therapeutic need, in this case the oligodendrocyte. Whether or not this proves a practical strategy for inducing the regeneration of myelinating oligodendrocytes in a demyelinated lesion,⁹³ it provides a valuable proof of principle for modulating the fate of endogenous progenitor cells as a means of restoring oligodendrocyte populations lost to injury, inflammation, or disease.

OVERVIEW AND CAVEATS

The persistence of neural stem and progenitor cells in the adult human brain provides us a set of fundamentally new opportunities for modulating the cellular composition of the injured or diseased adult brain. The induced regeneration of specific neuronal populations, such as the striatal neurons lost in Huntington's disease, has already been achieved in

rodents, and work proceeds apace in inducing the regeneration of both subcortical and cortical neuronal populations. Similarly, the mobilization of glial progenitor cells as a means of inducing remyelination of demyelinated foci may prove of seminal importance in treating diseases of central myelin. Furthermore, targeting these same progenitors to prevent their reactive astrocytic differentiation may serve to mitigate the complications of astrogliosis and glial scar formation, such as axonal regenerative failure and post-ischemic seizure disorders.

The attractiveness of modulating the turnover and fate of endogenous progenitors as a therapeutic strategy may be tempered, however, by concern as to the risks of dysregulated mitogenic expansion *in vivo*. Earlier attempts at mobilizing subependymal progenitors have been hindered by formation of periventricular nodules³⁹ and heterotopic gliosis,³⁸ which suggested early tumorigenesis, whereas analogous attempts to drive oligodendrocyte progenitor expansion have yielded gliomas. Indeed, resident stem and progenitor cells may be the source of primary brain tumors.^{94–97} As a result, more recent studies of induced neurogenesis⁵³ and oligoneogenesis⁹² have focused on modulating the differentiation of resident precursor cells, rather than their proliferative expansion. As our understanding of the therapeutic potential of targeting endogenous progenitor cells increases, *pari passu* with our appreciation of its potential risks, we can anticipate the development of a fundamentally new generation of both gene-based and pharmacotherapeutic strategies for treating diseases of the brain.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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